THE SYNTHESIS OF SOME GABA ANALOGUES: A CONTRIBUTION TO THE CHEMISTRY OF AMINOMETHYL-γ-LACTONES

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TO MY FAMILY

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ABSTRACT

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter of wide distribution in the central nervous system. The phthalideisoquinoline alkaloid, bicuculline, is an effective inhibitor of the GABA-neurotransmission and it is believed that the action is due to the presence of the aminomethyl-γ-lactone moiety of this molecule. This work was directed towards the synthesis of some neurophysiologically active compounds which can mimic the action of GABA. The design falls into three categories: (1) monocyclic γ-lactones where the aminomethyl group is at the α-, β - or γ -position of a lactone, (2) aza-heterocycles fused onto lactones and (3) sugar lactones with an aminomethyl group as part of the structure.

The β -aminomethyl-γ-butyrolactone salts [(120a) and (120b)] were prepared by three methods. First, the common intermediate, the hydroxy compound (117), was made by either the Wittig-Horner reaction of the diacetoxypropanone (109) with the phosphonate (112) or an oxidation-reduction sequence on the vinyl-γ-lactone (169) which was obtained by a Claisen rearrangement of a vinyl ether (167). This alcohol (117) was converted to the amine salts <u>via</u> the sulphonate (118) and the azide (119). Secondly, the hydrochloride salt (120a) was prepared by catalytic hydrogenation of the nitro compound (182) which was produced by the Michael addition of nitromethane to Δ^2-butenolide

(181) and also from the Michael adduct of the α,β-unsaturated ester, (187)→(188)→(189)→(182). Thirdly, the allylic bromide (200) was converted to the unsaturated azide (202) and then to (120a) by catalytic hydrogenation. A phthalimido derivative (203) was also synthesized from the bromide (200).

Two types of γ-aminomethyl-γ-butyrolactones were made. The optically active amino lactone (232) was obtained from L-glutamic acid by a stereospecific lactone formation reaction to afford the lactonic acid (225) which was transformed into (232) through the esterification, reduction, tosylation, azidolysis and hydrogenolysis sequence. One of the common intermediates, the alcohol (228), was also prepared from 2,3-isopropylidene-D-glyceraldehyde (260) by a Wittig-Horner reaction and followed by hydrogenation and acid catalyzed lactonization. The piperidinium salt (246b) was formed by the displacement of the tosylate (230) by piperidine and then passed through anion-exchange column. The diastereomeric azidomethyl-γ-lactone (251) was produced by either the azide displacement of the iodide (249) or the ring opening of the oxirane (257) to furnish the azido lactonic ester (259) and followed by decarboxylation. Reduction of the azide afforded the amine salt (252). In fact, this salt (252) could also be obtained by a one-step synthesis starting from the phthalimido epoxide (272) by reaction with diethyl sodiomalonate and followed by lactonization, decarboxylation and removal of the amino group protection with aqueous acid.

For comparison purposes, α-dimethylaminomethyl-γ-butyrolactone salt (299a) was successfully prepared by a literature method. However, attempts to obtain the parent amino compound (308a) <u>via</u> the alcohol, sulphonate and azide intermediates or by catalytic hydrogenation of the nitrile (306) failed.

An attempt was made to prepare the pyrrolidine-γ-lactone (316) <u>via</u> the intermediacy of the epoxide (314) failed. A further attempt of making the corresponding piperidine analogue by the same methodology also failed. However, an isomeric mixture of piperidine-lactones [(341) and (342)] could be obtained <u>via</u> diethyl pyridine-3,4-dicarboxylate through monosaponification, reduction of the ester group, lactonization and finally catalytic hydrogenation.

These primary and secondary ammonium salts were derivatized as the corresponding benzamides to facilitate the characterization of the hygroscopic salts.

In the sugar lactone series, 5-amino-5-deoxyribono-γ-lactone (349) was prepared using a reported procedure. The α,β-unsaturated δ-lactones [(357) and (358)] were synthesized from the 2,3-dihydroxygluconolactone (356) <u>via</u> β-elimination of acetic and tosic acids. However, the conversion of these α,β-unsaturated esters to branched-chain sugars by means of the Michael addition of nitromethane failed.

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DISCUSSION

INTRODUCTION

In this section of the thesis, some fundamental aspects of the central nervous system are mentioned before we touch upon the biology and chemistry of γ-aminobutyric acid (GABA) and its analogues.

(1) The neural pathways

The main structural units of nervous systems are nerve cells,[1] or neurones. Each typically consists of a nucleus-containing cell body and of one or more filamentous processes, or fibres extending away from the cell body (Figure 1). Nerve fibres that carry impulses towards the cell body are dendrites; those carrying impulses away are axons.

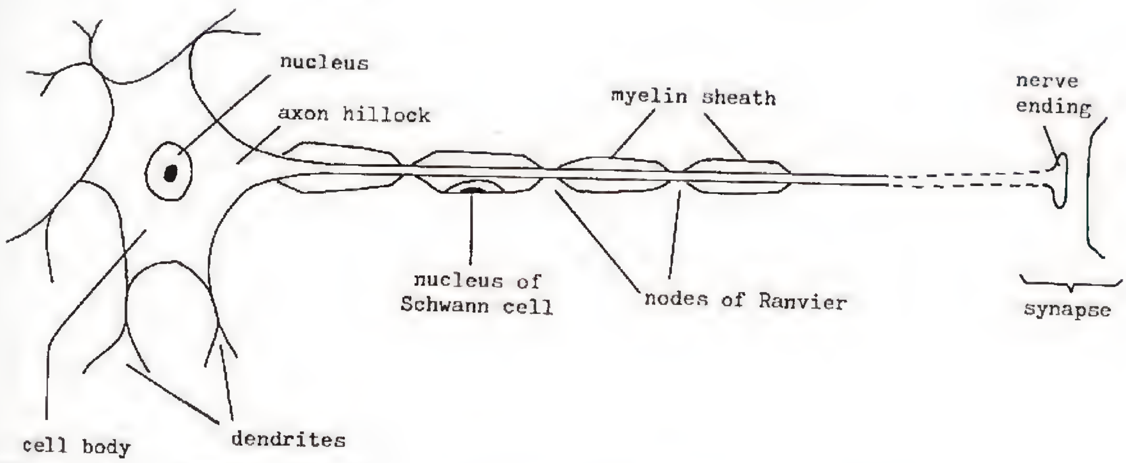


Figure 1 TYPICAL VERTEBRATE NEURONE

Adjacent neurones are not fused together structurally. They interconnect functionally at a synapse,

the region where the fibre terminals of the neurones come close to each other (Figure 2). According to their position within a reflex arc, sensory neurones transmit impulses from a receptor to a modulator, and motor neurones transmit from a modulator to an effector. Neurones within a modulator are known as interneurones. Groups of nerve fibres frequently traverse a body region as a single collective fibre bundle, or nerve. Nerves are designated as sensory, motor, or mixed, depending on whether they contain sensory fibres, motor fibres, or both.

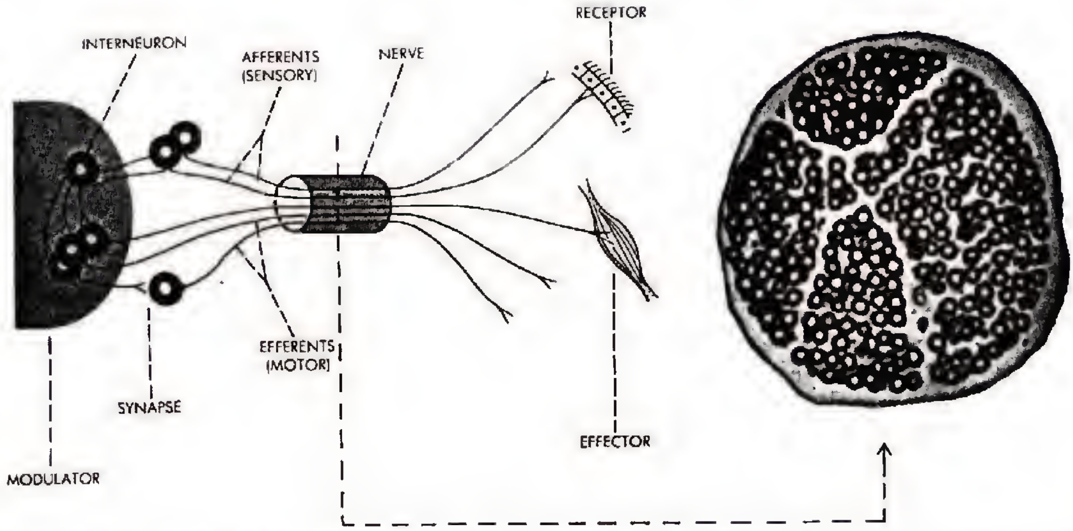


Figure 2 NEURAL PATHWAY PATTERNS

By far the most complex nervous systems are those of vertebrates. The main parts are an anterior brain, a posterior spinal cord, and the peripheral nerves connecting with these organs.[2,3] Within brain and spinal cord are interconnected, fluid-filled spaces, the brain ventricles and the spinal canal. The major divisions of the brain are the forebrain, the midbrain, and the hindbrain[2] (Figure 3). It has been recognized that dif-

ferent regions of the brain govern all sorts of important functions of the body.[4,5] For example, the olfactory lobes in the forebrain, are the centres for the sense of smell.

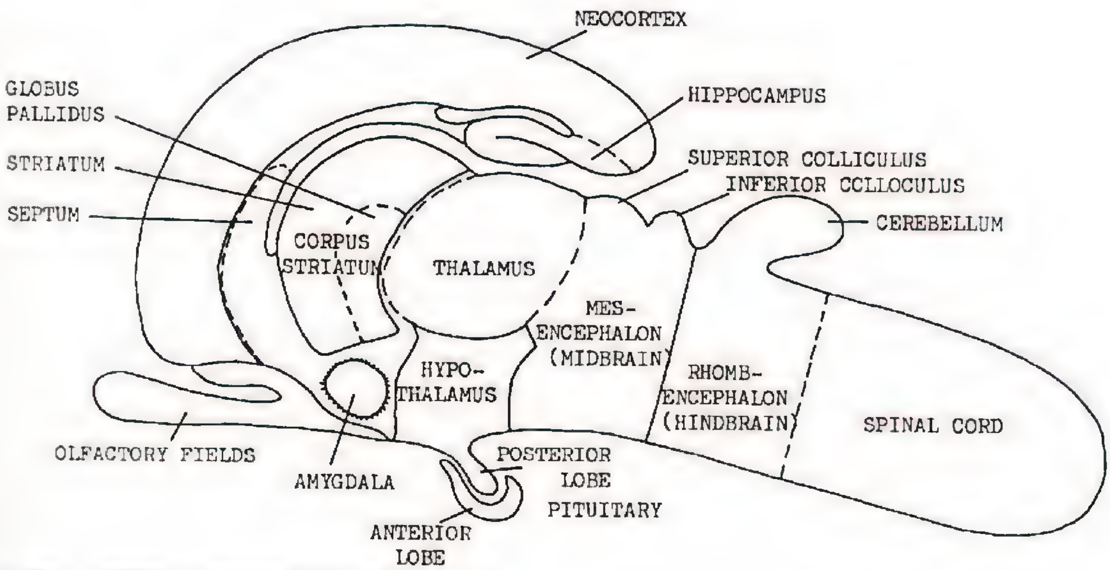


Figure 3 MAMMALIAN BRAIN AND SPINAL CORD - SCHEMATIC VIEW

There are also some areas of the brain which are of importance in neurochemistry[3], *e.g.*, the substantia nigra, and the limbic system.

(2) How a message is sent

(2.1) Electrical transmission in neurones

Because cell membranes are not equally porous to all cations and anions, most cells of the body have concentrations of these ions inside the cell which are different from those found in the extracellular fluids. The membranes of most cells appear to be quite permeable

to potassium and chloride ions[6,7] but they have a mechanism colloquially called the " sodium pump "[8,9] which keeps the intracellular sodium ion concentration considerably lower than that on the outside. Since the potassium ions remain inside the cell where they are electrostatically attracted to large electronegative non-permeating proteins, there is an imbalance in electrical charges. This imbalance results in the interior of the cell being electronegative compared to the exterior, and the electrical potential thus generated, which averages 70 mV, is known as the resulting membrane potential.

Electrical transmission within neurones begins with a sudden, localized and transient increase in membrane permeability to sodium ions, an increase which is believed to arise from the loss of calcium ions from the pores in the membrane. This increase in permeability leads to a diffusion controlled influx of sodium ions. Some potassium ions are consequently displaced, but as the rate of efflux of potassium ions is very much slower than the rate of influx of sodium ions, the membrane potential is reversed as the inside of the cell becomes positive relative to the outside. In this condition the neuronal membrane is said to be polarized. As the sodium pump re-asserts itself the sodium ions are pumped out and the polarity reverts to normal. The resultant changes in membrane potential is shown on the diagram (Figure 4).

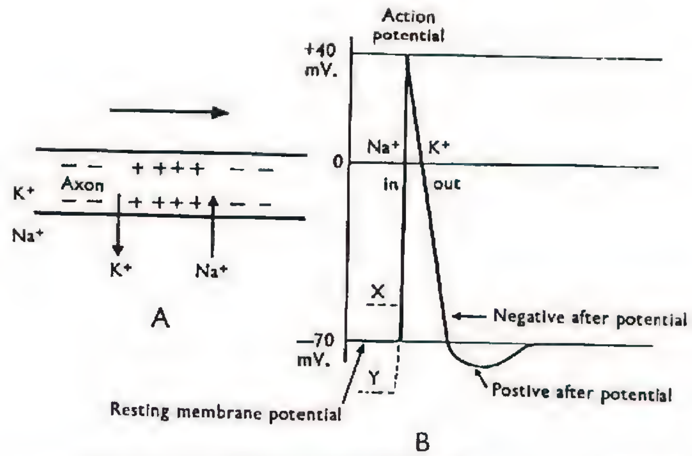


Figure 4 CHANGES IN MEMBRANE POTENTIAL DURING DEVELOPMENT OF AN ACTION POTENTIAL

The action potential moves down an axon, because, all along the length of a non-myelinated axon, there are channels which are selectively permeable to either sodium or potassium ions. The action potential is triggered by a signal from the cell opening a sodium channel which allows sodium ions into the cell thus reversing the polarity. The existence of the action potential then closes the sodium channel, opens the potassium channel and reverses the ion flow. Moreover, the presence of an action potential in one part of the axon opens sodium channels in an adjacent part and this propagates the action potential along the axon. After a suitable interval of time, the process can be repeated. In myelinated neurones, the process is similar except that the exchange of ions only takes place at the nodes of Ranvier (Figure 1) and the action potential has to jump between adjacent nodes.

Since the value of the action potential is essentially controlled by the molecular properties of the neuronal membranes, this cannot be altered for a given system. The only mechanism for varying the degree of response is to alter the number of impulses generated in a given time. The arrival of the action potential at the synapse releases the neurotransmitter (see later).

(2.2) The synapse

The concept that neural pathways are interrupted at specific junctional points, was derived first from the physiological observation that there is an irreducible delay period inherent in reflex responses to sensory stimuli, and that neural conduction occurs only in certain directions.[10] In the advance of electron microscopy, a considerable amount of physiological and pharmacological knowledge has been correlated with the morphological basis of synapses and their molecular organization. Since individual chemical synapses conduct only in one direction, some type of asymmetry might be expected in their structure. The most common type of synaptic junction is that between an axon and a dendrite or a soma. Electron micrographs of typical synapses[11] are shown below (Figure 5).

Figure 5 ELECTRON MICROGRAPHS OF SYNAPSES IN CAT OCULO-MOTOR NEUCLEUS.
A presynaptic terminal (A) makes synaptic contact with a large cell body (S), and under this synapse are a number of postsynaptic dense bodies (1). The insets show a similar synapse on a cell body and on a dendrite (D). Magnification X 30,000 (insets, X 50,000). (From Pappas and Waxman, 1972.)

(2.3) Chemical transmission

The synaptic junction is a gap of some 200-500 Å wide. It is represented here in a diagrammatic scheme indicating the multiple sites of drug action at a GABA synapse[12] (Figure 6).

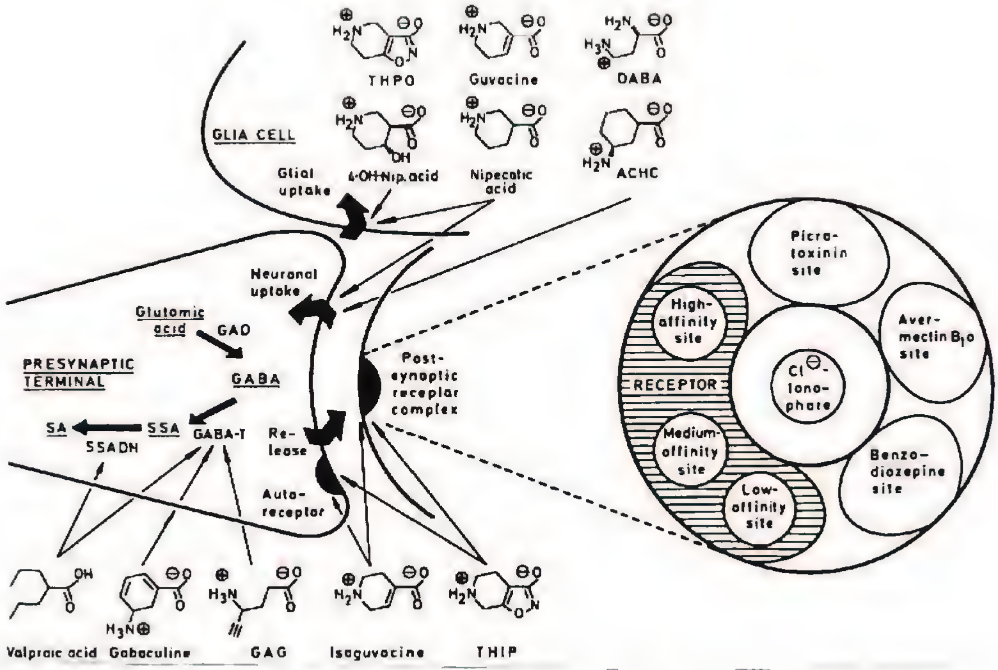


Figure 6 AN ILLUSTRATION OF THE PROCESSES AND THE RECEPTOR COMPLEX IN A GABA SYNAPSE AND OF THE SITES OF ACTION OF VARIOUS GABA ANALOGUES (REFERENCE 12)

The neurotransmitters are synthesized in the neurone, then stored in vesicles to prevent their degradation by the enzymes present in the cytoplasm of the axon.[13] The vesicles migrate to the cell membrane at the synapse and as a result of the neuronal impulse transmitted by the axon the contents are released into the synaptic cleft. The neurotransmitter diffuses across the gap and combines with its own specific site known as a receptor on the other side of the cleft. The process of combining with the receptor then initiates a response in the second tissue, the nature of the response depending on the precise location of the synapse.[13] If the synapse lies between two neurones, the response may be to initiate or prevent a subsequent nerve impulse.

In the first case the process is said to be excitatory; in the second, it is inhibitory.

In both these situations, however, the very different responses are believed to arise from the chemical to receptor interaction affecting the character of the cell membrane. In particular, alternations in the permeability of the membrane to inorganic ions, such as sodium, potassium and calcium are strongly implicated. After the initiation of the effect, the neurotransmitter is released from its receptor and deactivated in a number of ways. For some neurotransmitters, most notably acetylcholine, enzymes are present in close proximity to the cleft which can metabolize the transmitter. For others, the presynaptic axon or the associated glia cell has specific uptake processes which absorb the released transmitter. Frequently, the neurotransmitter is removed by diffusion into the extracellular fluids.

The role of the synapse is to allow a graded response to occur in the system with a finite limit. The response to a neurotransmitter is directly related to the amount interacting with the receptor, the existence of a finite number of receptors preventing the system being overloaded.

(2.4) Neurotransmitters

Historically, the pioneering concept of chemical

transmission was first expressed by Du Bois Reymond (1877) and by Loewi (1903)[14,15]. However, the most convencing proof of the chemical theory was shown experimentally in ca. 1930's and 1940's for acetylcholine and catecholamine transmissions not only in smooth muscles, and finally in the central nervous system as well, by investigators, including Dale, Feldberg, Krayer, Cannon, Voigt, Bacq and von Euler.

(2.4.1) Identification of neurotransmitter candidates

A substance is only valid to be called a transmitter of a certain synaptic connection if the following criteria have been established[16].

(a) if it is present in presynaptic elements of neuronal tissue;

(b) if precursors and resultant enzymes are present;

(c) if it is released from the presynaptic nerve;

(d) if there is a special receptor present;

(e) if an antagonist can halt interaction of the substance with its receptor and agonist acts otherwise[17].

(2.4.2) Neurotransmitter candidates

They may be classified as inhibitory or excitatory, depending on the electrophysiological response to

them.[15,18-20] Some of the more important compounds are listed in Table 1.

TABLE 1

NEUROTRANSMITTER SUBSTANCES

Transmitter	Synonyms	Abbreviation
Acetylcholine	-	ACH
Dopamine	-	DA
Gamma aminobutyric acid	-	GABA
Glutamic acid	-	Glu
Glycine	-	Gly
5-Hydroxytryptamine	Serotonin	5-HT
Norepinephrine	Noradrenaline Arterenol	NE

(3) γ-Aminobutyric acid (GABA) : the CNS neurotransmitter

(3.1) Discovery and distribution

The presence of the neutral amino-acid, γ-aminobutyric acid [GABA, (1), see p. 16] in extracts of brain tissue was first demonstrated in 1950,[21,22] but its potency as a central nervous system (CNS) depressant was not immediately recognized. In the crustacean stretch receptor, GABA mimicked the actions of stimulation of the inhibitory nerve. Kravitz and coworkers[23] demonstrated that GABA was the only inhibitory amino-acid

found exclusively in the inhibitory nerve in the crustacean and that the inhibitory potency of extracts of this nerve were accounted for by their content of GABA. Release of GABA was then correlated with the frequency of nerve stimulation. Intracellular recordings from the muscle indicated that the inhibitory nerve and GABA produced identical increases of Cl^- conductance in the muscle. These observations (see previous section on identification of neurotransmitters) thus fully satisfied the criteria for a transmitter by Otsuka[24] in 1973. It was proposed to be a CNS postsynaptic inhibitory transmitter in 1975.[25]

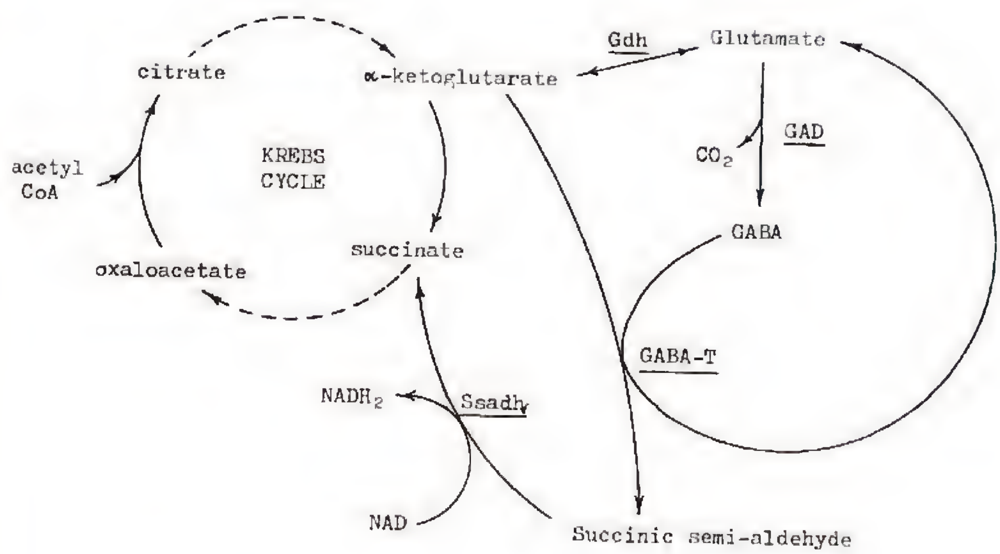
These same physiological and pharmacological properties were later found to be useful models in tests of a role for GABA in the CNS. Evidence strongly supports the idea that GABA mediates the inhibitory actions of local interneurones in the brain regions rostral to the spinal cord, and that GABA may also mediate presynaptic inhibition within the spinal cord.[24,26] Presumptive GABA-ergic inhibitory synapses have been demonstrated most clearly between cerebellar Purkinje neurones and their targets in Deiter's nucleus; between small interneurones and the major output cells of cerebellar cortex, olfactory bulb, hippocampus, and the lateral septical nucleus. GABA may also mediate the effects of inhibitory neurones within the cerebral cortex.[27] The existence of a GABA-ergic pathway from caudate nucleus to substantia nigra is supported by neuro-

chemical and cytochemical evidence.[27–30]

(3.2) The synthesis and metabolism of GABA within a presynaptic neurone

This is represented by the so-called " GABA shunt " (Figure 7).

As can be seen from the diagram, glucose from outside the neurone is the fundamental precursor of GABA, through the tricarboxylic acid cycle[31] and eventually produces the starting material, glutamic acid, which is decarboxylated to GABA. The extensive literature on this subject has been summarized in a series of reviews.[30,32-34] Recently there was also a chemical study on the stereochemical course of the formation of GABA by decarboxylation of (2S)-glutamic acid.[35]



Enzymes: Gdh = glutamate dehydrogenase
GAD = glutamate decarboxylase
GABA-T = GABA-glutamate transaminase
Ssadh = succinic semi-aldehyde dehydrogenase

Figure 7 " GABA SHUNT " IN NERVOUS TISSUE

(3.3) Pharmacological interventions in the GABA system

Based on the available information concerning the complicity of GABA in various diseases, decreased function of the GABA system contributes to the pathogenesis of these CNS illnesses.[36] So far hyper-activities of GABA synaptic processes have not been demonstrated in any diseases. Consequently strategies for pharmacological manipulations of GABA synaptic mechanisms must aim at stimulation of GABA neurotransmission.[12,37] The different steps involved in the course of GABA synaptic transmission (see Figure 6) (p.8) have been extensively studied,[36b-d,37,38] but our knowledge of the mechanism of action of GABA at the molecular level in different synaptic process is still very incomplete.

The synthesis of GABA from glutamic acid is catalyzed by GAD, and GABA is transformed into succinic semialdehyde (Ssa) by GABA : 2-oxoglutarate aminotransferase (GABA-T).[39] Activitation of the receptor-ionophore complex by GABA results in inhibition of the firing of the postsynaptic cell via hyperpolarization of the cell membrane.[13b] The synaptic transmission is terminated by transport of GABA from synaptic cleft into nerve terminals and glia elements via high affinity uptake systems. Extracellular enzymatic degradation of GABA apparently is not involved in the termination of GABA neurotransmission.[37]

There are several potential pharmacological

sites of attack in the GABA synapses.[12,37] A few of the principles and possibilities for stimulation of GABA neurotransmission _via_ pharmacological intervention of various synaptic processes are summarized as below:-

(a) use of GABA-T inhibitors;
(b) inhibitors of GABA uptake;
(c) GABA receptor agonists;
(d) GABA receptor antagonists.

(3.4) Functions of GABA and its dysfunctions in relation to neurological and psychiatric disorders

GABA is involved in the regulation of many physiological functions,[36b] including blood pressure and heart rate,[40] secretion of prolactin and other hormones,[41] and sensation of pain[42] and anxiety.[43] It is also known that some drugs may act on GABA-mediated inhibition, _e.g._, benzodiazepines,[43e] bacleofen,[44] barbiturates,[45] butyrophenones,[46] morphine[47] and alcohol.[48]

Dysfunctions of the GABA system have been recognized as the causes of some neurological and psychiatric disorders,[36] _e.g._, Huntington's chorea, Parkinson's disease, Schizophrenia and epilepy.

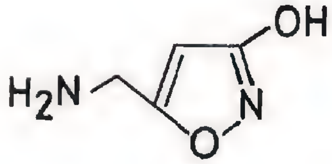
(4) GABA analogues

The study of neurotransmitters in both central and peripheral pathways is generally facilitated by the

$H_2NCH_2CH_2CH_2CO_2H$

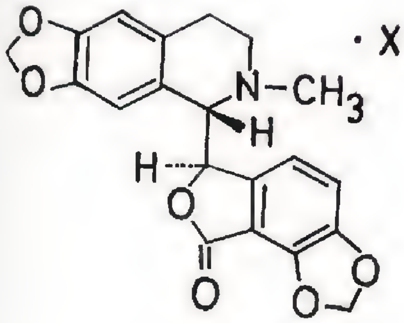
GABA

(1)



Muscimol

(2)

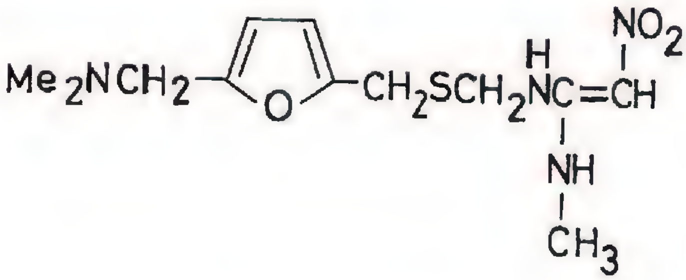


(+)-Bicuculline

a : X = nothing

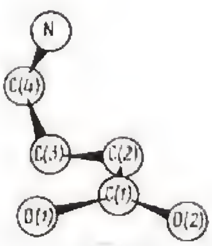
b : X = HCl

(3)



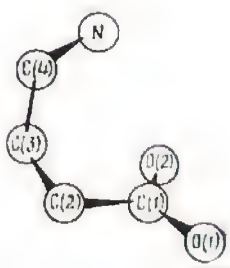
Ranitidine (AH19065)

(4)



Extended structure of GABA

(5)



Folded structure of GABA

(6)

use of selective agonists and antagonists, for example, acetylcholine,[49] catecholamines[49c,50] and morphine-reated analgesics.[51] For γ-aminobutyric acid [GABA,(1)], it is possible to find agonists and antagonists from natural sources, e.g., muscimol[52](2) and bicuculline[53] (3) from the plant kingdom. These compounds can be used to study the behaviour of GABA receptors.[54] Useful information has been gained from structural-activity-relationship studies with other neurotransmitters.[55] A recent study has led to the discovery of drugs acting at the H_2 receptors[56] [e.g., ranitidine (4), anti-ulcer drug]. In this connection, the question of the influence of the stereochemistry of GABA on its biological and pharmacological activities assumes considerable importance.[57]

The stereochemistry of GABA and its analogues has been well studied.[54b,58] Compounds prepared have usually been based on the structure of GABA in which some structural feature is systematically varied or in which conformational flexibility is restricted (e.g., in acetylcholine analogues[49]). In fact GABA can exist in a wide variety of shapes. At least two of them are recognized to be the most important conformations, namely the extended and folded structures[58a] [(5) and (6)].

The conformational mobility can be reduced in analogues of GABA by the incorporation of bulky substituents, unsaturation, carbocyclic rings, hetero-

cyclic rings, or combinations of these. Furthermore, interactions with various receptors can be hindered or facilitated by the presence of particular functional groups at certain positions. Such interaction can be investigated systematically by ideas in drug design[59] such as isosteric replacement of functional groups in a drug molecule so that the modified compound will act at the same receptor site. The manipulation of the structure of GABA according to these ideas has well been studied in dealing with synthesis of its analogues.[54b,54d-f,60] The following is a tabulation of some of the analogues and their reported biological activities (Table 2).

TABLE 2

Compounds	No.	Neurophysiological activities	References
β-alanine	7	relatively active GABA agonist	61
6-aminohexanoic acid	8	inactive as an agonist	62
3-aminopropane-sulphonic acid	9a	selective GABA agonist	63
3-aminophosphonic acid	9b	weak receptor agonist	64
3-aminoboronic acid	9c	inactive	62

TABLE 2 (cont.)

Compounds	No.	Neurophysiological activities	References
N-hydroxy-4-aminobutyramide (i.e.,γ-amino-butyrohydroxamic acid	9d	weak inhibitor of GABA-T	65
cetyl-GABA (and other esters)	9e	anticonvulsant agent	66
N-dodecyl-4-aminobutyramide	9f	GABA uptake inhibitor	67
ethanolamine-O-sulphate	10	irreversible inhibitor of GABA-T	68
ethylenediamine	11	selective glia GABA uptake inhibitor	69
3-guanidinopropionic acid	12	potent on GABA receptor assays	70
N-benzoyl-GABA	13	has anticonvulsant activity	71
sodium 4-hydroxybutyrate	14	effective in CNS	72
3-hydrazino-propanoic acid	15a	potent inhibitor of GABA-T	73
3-aminooxy-acetic acid	15b	inhibitor of GABA-T	74
4-methyl-GABA	16	moderately potent on GABA binding and uptake	75

TABLE 2 (cont.)

Compounds	No.	Neurophysiological activities	References
β-(*p*-chlorophenyl)-GABA (baclofen)	17	acting on CNS; depressant of spinal cord; (-)-isomer is more active than (+)-isomer	76
2-amino-GABA	18	potent GABA inhibitor; (S)-(+)-isomer is more active as inhibitor for GABA neuronal uptake	77
3-hydroxy-GABA (GABOB)	19	potent inhibitor of GABA uptake	78
5-aminolevulinic acid	20	weakly active	79
3-amino-2-oxopropane-sulphonic acid	21	as potent as GABOB at inhibiting GABA binding	80
cis and *trans*-4-amino-crotonic acid	22 (a,b)	*trans*-isomer is more active as an agonist on binding site and GABA-T inhibitor	81
4-aminotetrolic acid	23	weak inhibitor of GABA uptake; inhibitor of GABA-T	82
γ-acetylenic GABA	24	irreversible GABA-T inhibitor	83
γ-allenic GABA	25	not tested	84

TABLE 2 (cont.)

Compounds	No.	Neurophysiological activities	References
(S)-4-amino-5-hydroxypentanoic acid	26	time-dependent, irreversible inactivator of GABA	85
progabide (SL76002)	27	a GABA-mimetic compound	86
2-aminomethylcyclopropanecarboxylic acid (and other carbocyclics)	28 (a,b)	GABA agonist; *trans*-isomer is more active than the *cis*-isomer	87
3-aminocyclohexanecarboxylic acid	29	*cis*-isomer is a selective inhibitor of GABA uptake	88
Gabaculine	30	potent inhibitor of GABA-T	89
3-aminobenzoic acid	31	inactive	58b
β-proline	32	low GABA-mimetic activity on uptake	90
pyrrolidin-3-ylacetic acid	33	equipotent with GABA as a neuronal and glial uptake inhibitor	91
kainic acid	34	neuroexcitatory activity (glutamic acid agonist)	92

TABLE 2 (cont.)

Compounds	No.	Neurophysiological activities	References
phenylpyrrolidone	35	increase the amplitude of induced potentials in postganglionic fibres	93
benzylpenicillin	36	GABA antagonist	54f & 94
4-methyl-ε-caprolactam	37	possesses CNS and convulsant activities	54f & 95
γ-butyrolactone (β-aryl-γ-butyrolactones)	38a (38b)	slows the firing rate of dopaminergic neurones (psychotropic agent)	54e & 96a-b (96c)
α-(substituted amino)-γ-butyrolactones	39	has anticonvulsive and sedative effects and also as strychnine antagonists	97
3-aminobenzylphthalides (and other aminomethylphthalides)	40	weak CNS activity (also tested as analgesics)	98
D,L-β-aminomethyl-γ-(p-chlorophenyl)-γ-butyrolactone	41	CNS depressant activity	99
5-(aminomethyl)-3-hydroxyfuran-2(5H)-one	42	showed negligible activity as a GABA agonist	100

TABLE 2 (cont.)

Compounds	No.	Neurophysiological activities	References
securinine* (and other lactonic alkaloids)	43a (43b -c)	showed strychnine-type activity and is a GABA receptor antagonist	101
pilocarpine (and analogues)	44	has cholinergic activity	102
cis-1-methylpiperidine-4,3-acetolactone methiodide	45	showed a weak atropine-like antagonistic effect to acetylcholine	103
nipecotic acid	46	potent and selective inhibitor of GABA uptake	104
isoguvacine	47	selective GABA agonist	105
piperidine-4-sulphonic acid	48	GABA agonist; not affecting GABA uptake	106
muscimol	2	potent agonist; weak inhibitor of GABA uptake; not a substrate for GABA-T	107
4,5,6,7-tetrahydroisothiazolo[5,4-c]pyridin-3-ol (THIP)	49	GABA agonist; possesses analgesic properties	108

* Footnote (see p. 25)

TABLE 2 (cont.)

Compounds	No.	Neurophysiological activities	References
5,6,7,8-tetrahydro-4H-isoxazolo[3,4-d] azepin-3-ol (ISOTHAZ)	50	GABA antagonist	109
5-(2-aminomethyl) hydantoin	51	almost inactive	110
quisqualamine	52	CNS depressant	111
Kojic amine (and derivatives)	53	a GABA-like compound	112
t-butylbicyclophosphate	54	GABA antagonist	113
tetramethylenedisulphotetramine	55	GABA antagonist	114
valproic acid	56	anticonvulsant	115
2,6-c-dimethyltyrosine-D-amino acid-γ-aminobutyramide	57	analgesic	116
avermectin A_{1b}	58	anthelmintic; believed to interfere with the GABA transmission	117

Footnote:

* Securinine (43a) was first located in a Chinese publication[101a] on the more recent pharmacology of this compound in August, 1981. Due to the similarity of this substance to one of the conformational structures of GABA, it was felt that the strychnine-type of activity of this compound might be a wrong interpretation, and it might be due to a GABA antagonistic effect.[118] Attempts were made to get hold of some of this alkaloid but were in vain. Recently, a communication was published by a joint American-Australian team under the leadership of Professor Curtis.[101b] It has been demonstrated that securinine is a stereospecific GABA receptor antagonist of restricted conformation [i.e., a classical receptor antagonist, which can block the bicuculline-sensitive receptor; a $GABA_B$ receptor antagonist is one that inhibits the bicuculline-insensitive receptor, which is agonized by baclofen[43a] (17)]. This leads to the speculation that the other lactonic alkaloids : tuberstemonine and related compounds[101c] [e.g., stemoninine (43b), isostemotinine .... etc] and dendrobine (43c) may possess GABA activity. One interesting point about the structure of dendrobine is that it has an aminomethyl-γ-lactone moiety like securinine and also contains the cage structure of picrotoxinin (59).

$H_2NCH_2CH_2CO_2H$

(7)

$H_2N(CH_2)_5CO_2H$

(8)

$H_2N(CH_2)_3X$

a : X = $\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}OH$; b : X = $\underset{\underset{OH}{|}}{\overset{\overset{O}{\|}}{P}}-OH$

c : X = Bo_2OH ; d : X = $\underset{\underset{O}{\|}}{C}\underset{\underset{H}{|}}{N}OH$

e : X = $\underset{\underset{O}{\|}}{C}O\text{-cetyl}$; f : X = $\underset{\underset{O}{\|}}{C}\underset{H}{N}-C_{12}H_{25}$

(9)

$H_2NCH_2CH_2O\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}OH$

(10)

$H_2NCH_2CH_2NH_2$

(11)

$H_2N-\underset{\underset{NH}{\|}}{C}-NHCH_2CH_2CO_2H$

(12)

$Ph\underset{\underset{O}{\|}}{C}\underset{\underset{H}{|}}{N}(CH_2)_3CO_2H$

(13)

$HOCH_2CH_2CH_2CO_2Na$

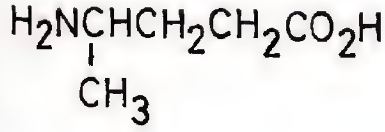
(14)

XCH_2CO_2H

a : $X = H_2N\underset{H}{N}-CH_2$

b : $X = H_2NO$

(15)



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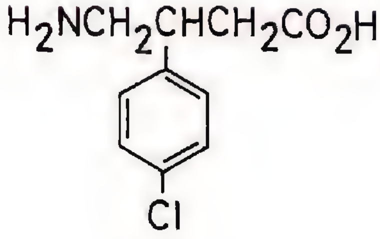

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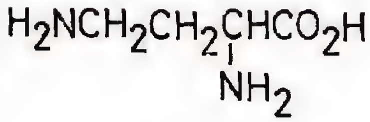

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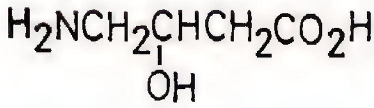

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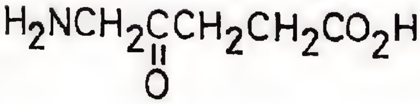

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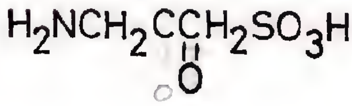

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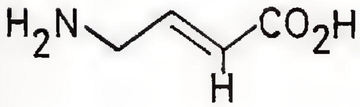
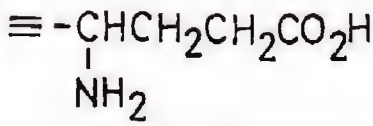


(22a)

(22b)

$H_2NCH_2-C\equiv C-CO_2H$

(23)



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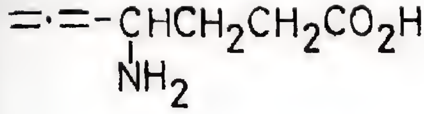

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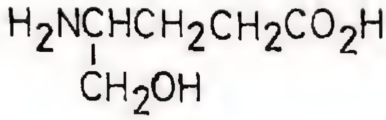

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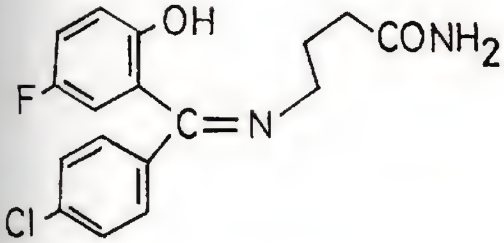
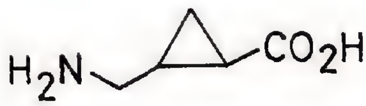
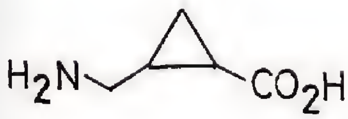


Progabide (SL76002)

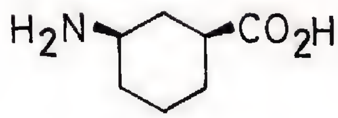
(27)



(28a)



(28b)



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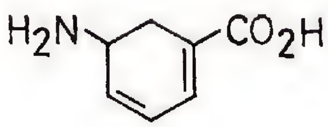

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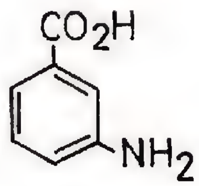

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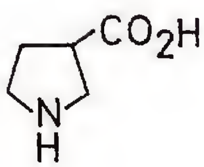

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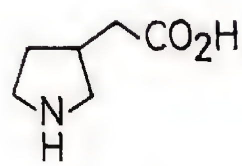

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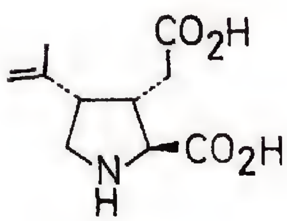

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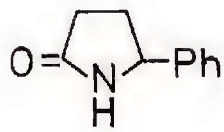

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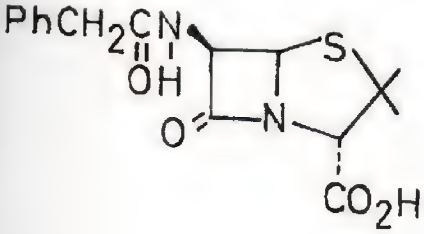

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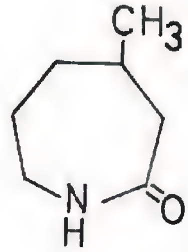

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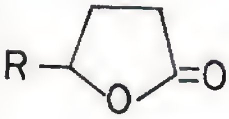
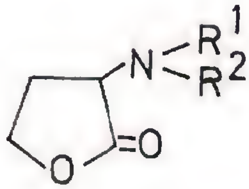
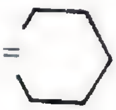


(38) a : R = H
b : R = Ph



R^2 = H ; a : R' = $\underset{\underset{O}{\|}}{C}O\text{-}{}^{n}Bu$

R^2 = H ; b : R' = $\underset{\underset{O}{\|}}{C}Ph$

c : R' = R^2 = 

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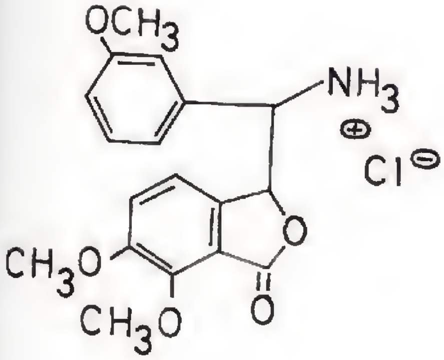

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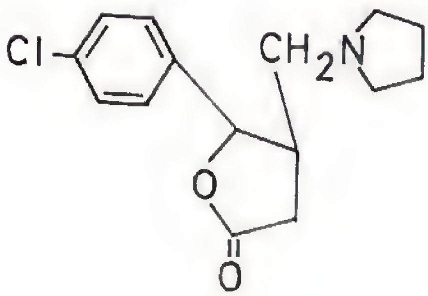

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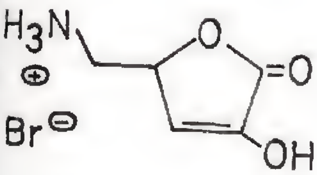
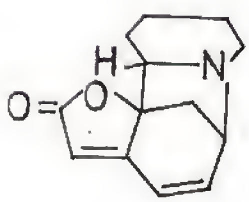
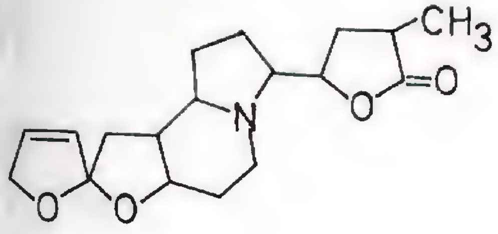


(42)

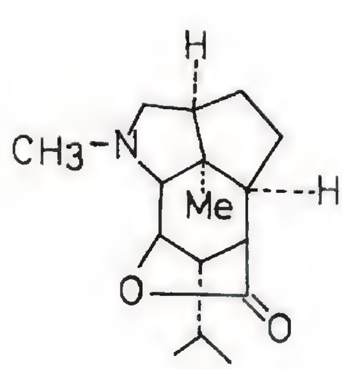


Securinine
(43a)



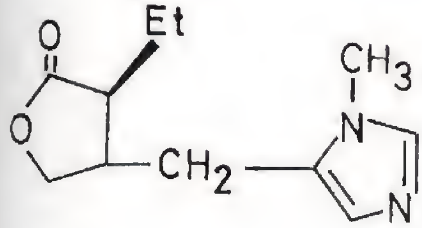
Stemoninine

(43b)



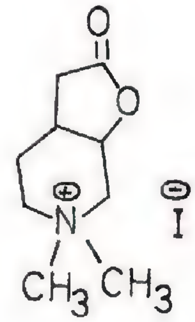
Dendrobine

(43c)

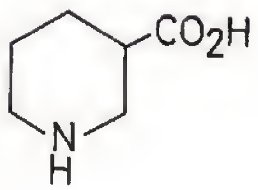


Pilocarpine

(44)

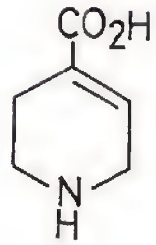


(45)



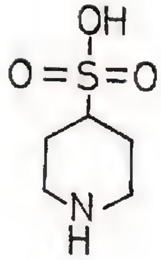
Nipecotic acid

(46)



Isoguvacine

(47)



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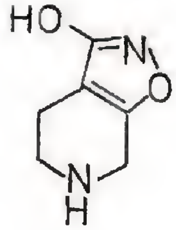
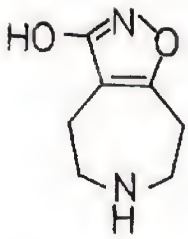


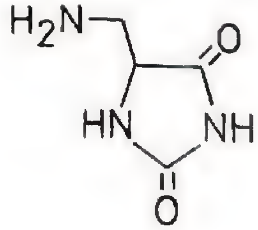
THIP

(49)



ISOTHAZ

(50)



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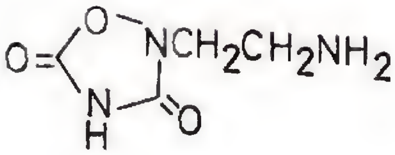
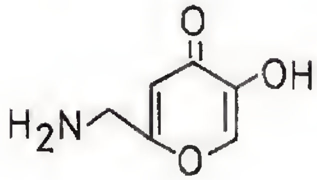


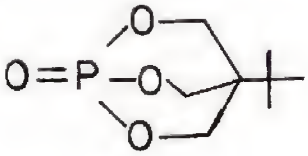
Quisqualamine

(52)



Kojic acid

(53)



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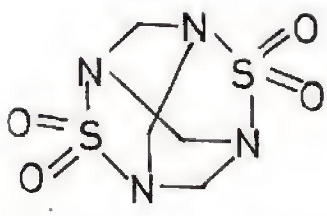

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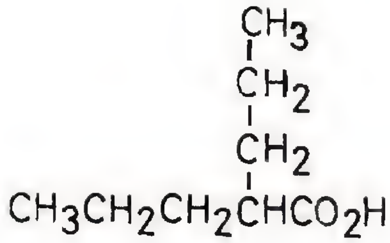
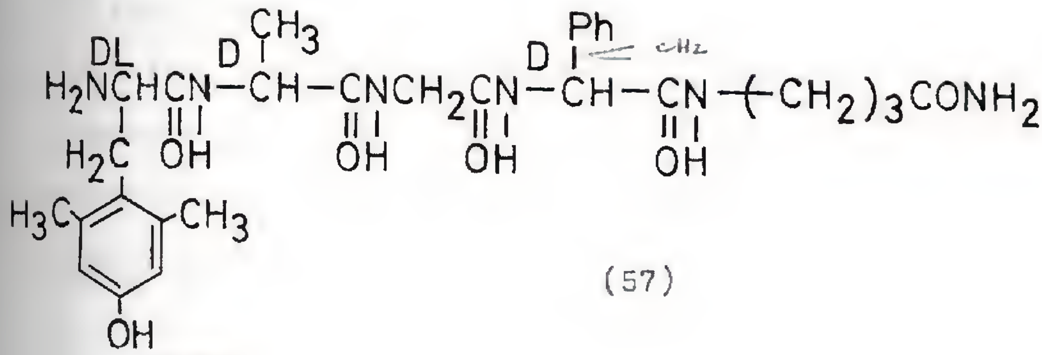


(56) Valproic acid



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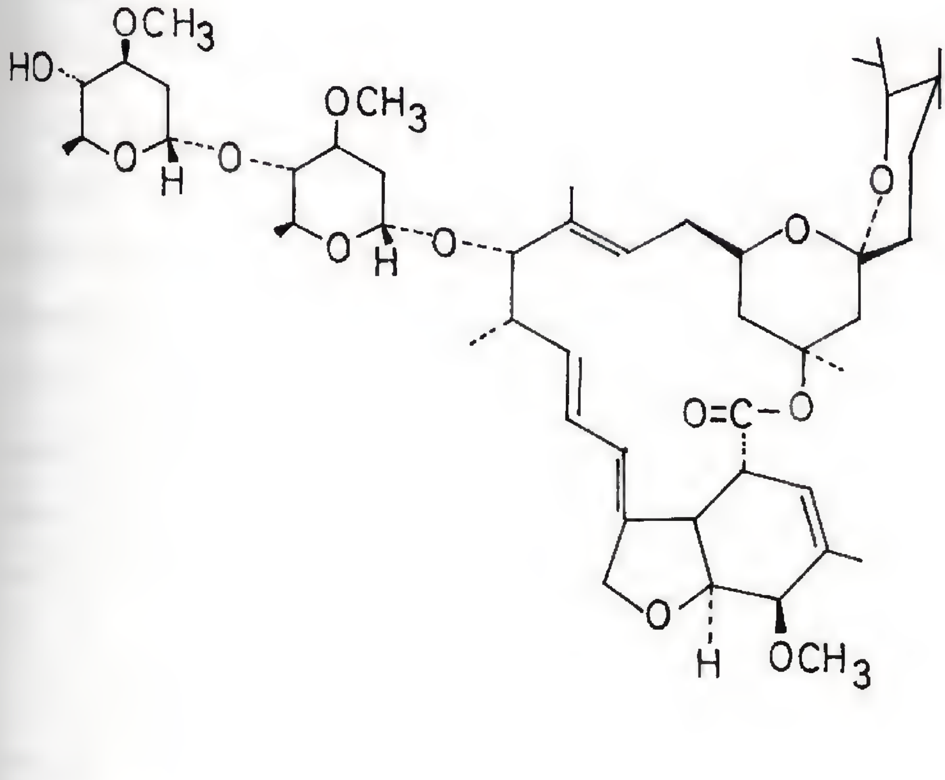


(58) Avermectin A_{1b} .

(4.1) γ-Lactones as GABA antagonists

GABA antagonists, which can induce seizures and convulsions in animals, are invaluable tools for pharmacological characterization of GABA receptors.[54a] In fact, there are at least two kinds of mechanism controlling the postsynaptic receptor complex, namely, the receptor and the picrotoxinin sites[119] (see Figure 6) (p.8). The two main classes of chemicals which are responsible for these functions are the phthalideisoquinoline alkaloid, bicuculline (3) (p.16) and the sesquiterpene, picrotoxinin (59) (p.37).

(4.1.1) (+)-Bicuculline (3)

Bicuculline as the hydrochloride and its more soluble methochloride salt are the most commonly used GABA antagonists. Some other phthalideisoquinoline alkaloids, such as corlumine (60) and hydrastine, are active antagonists.[58a] Opening the lactone ring in bicuculline leads to inactive bicucine. However, esterification of the carboxy group restores activity,[60a] as in bicucine methyl ester hydrochloride (61).

Since the discovery that bicuculline is a specific GABA antagonist, many theoretical and experimental studies have been made to determine the precise structural relationship between GABA and its receptor.[120] The antagonistic properties of bicuculline in relation to GABA were attributed to the alkaloid

molecule being isosteric with the biologically active conformation of GABA, enabling the bicuculline molecule to compete successfully with GABA for a portion of its receptor. The absolute configuration of crystalline bicuculline has been determined by X-ray crystallography[121] (Figure 8). The relative configurations of the asymmetric carbon atoms in the molecule are of greatest interest. The central part of the bicuculline molecule is illustrated schematically in Figure 8b, which can be compared with the GABA molecule (Figure 8c). It has been established that in this conformation of crystalline bicuculline the $N_{(6)}$ and $O_{(3)}$ atoms are antiperiplanar (almost _trans_) in relation to the $C_{(4)}$ - $C_{(5)}$ bond. The fully extended form of GABA requires only a slight constraint in order to correspond to the bicuculline conformation in the crystalline state. The carboxy group of GABA is isosteric with the group of $O_{(1)}$, $O_{(2)}$ and $C_{(26)}$ atoms of bicuculline. The configuration of bicuculline corresponding to the extended form of GABA is consistent with data obtained in a study[122] of the steric structure of one of the crystalline forms of the Copper(II) complex of GABA. Furthermore, the configuration of bicuculline salts [_e.g._(3b)] were shown to be analogous to the extended structures of GABA (Figure 9).

The part of the bicuculline molecule isosteric with GABA contains two asymmetric centres[123], giving four possible stereoisomers. Studies indicated that

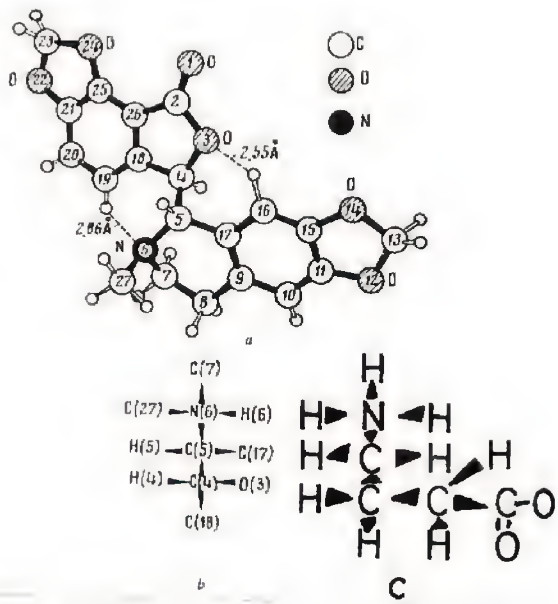


Figure 8 THE CONFIGURATION OF BICUCULLINE IN THE CRYSTAL : a) absolute configuration; b) relative configuration of the asymmetric atoms of the protonated molecule (the numbering of the atoms is in accordance with Gilardi's paper[121a]; c) zwitterionic GABA, with the same configuration.

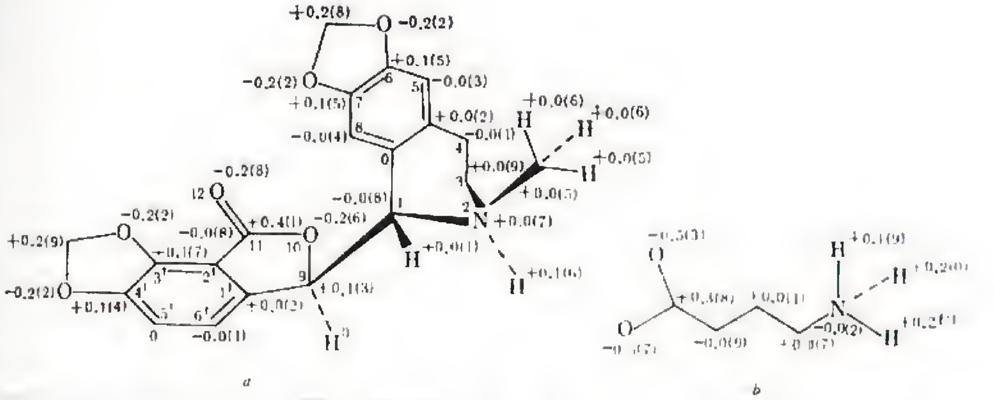


Figure 9. THE DISTRIBUTION OF CHARGES IN BICUCULLINE AND GABA : a) protonated bicuculline (in the conformation preferred for a solution of the alkaloid; b) GABA zwitterion (the numbering of the atoms is in accordance with the paper of Steward et al.[121c]).

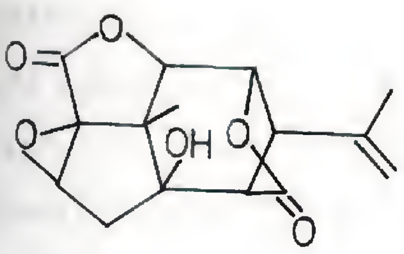
the (+)-bicuculline, which has the (1S, 9R)-configuration, exhibits a physiological GABA inhibiting activity and is more powerful than the (-)-isomer.

(4.1.2)Picrotoxinin (59) and analogues

Picrotoxin is an equimolar mixture of picrotoxinin (59) and its hydrated derivative, picrotin, the latter compound being approximately 50 times less potent than the former (59) as a convulsant. The natural products, such as coriamyrtin (62) and tutin share the convulsant action of picrotoxin but are also nonionic in solution. Unlike bicuculline (3), picrotoxinin appears to act at GABA regulated membrane chloride channels[119] rather than at the GABA receptors of the GABA receptor-ionophore complex (Figure 6), consistent with the non-competitive nature of its antagonism.

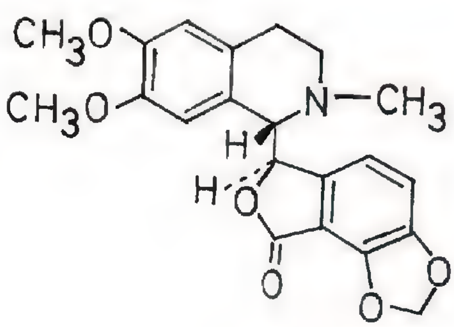
The total synthesis of picrotoxinin,[124] picrotin[125] and the other sequiterpenoid lactones[126] has been achieved. Other lactones, e.g.,(63) and β-ethyl-β-methyl-γ-butyrolactone [β-EMGBL, (64)] were prepared as convulsants.[127] Presumably, they performed as picrotoxin analogues.

In this thesis, the majority of work was based on the investigation of the preparation of aminomethyl lactones. These analogues were structurally related to the pharmacophoric fraction of bicuculline (3). They could be interpreted as analogues of GABA in the extended or folded forms. With this in mind, the syntheses were carried out under the following guidelines: (1) γ-, β- and α-aminomethyl-γ-butyrolactones were made; (2) compounds containing azaheterocycles fused with γ-



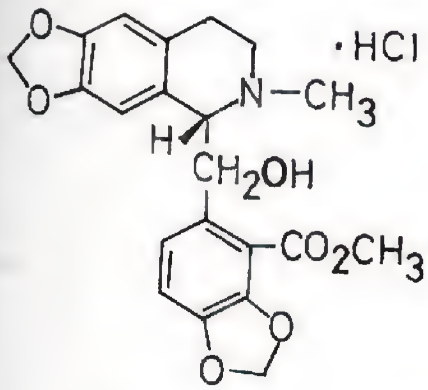
Picrotoxinin

(59)



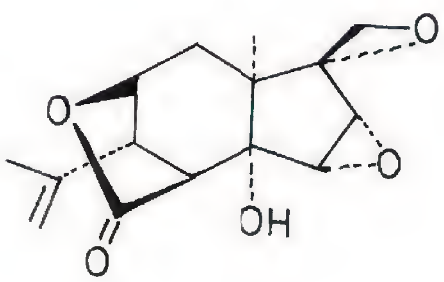
Corlumine

(60)



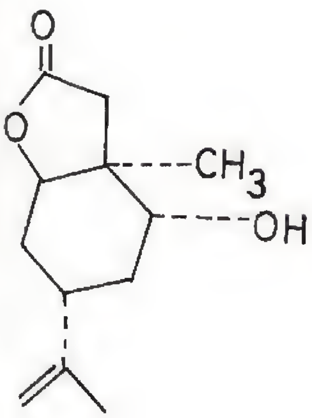
Methyl ester of bicucine

(61)

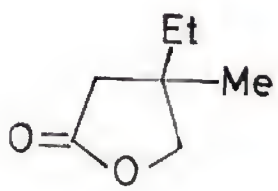


($\pm$) Coriamyrtin

(62)



(63)



β-EMGBL

(64)

butyrolactones, so constructed that they could satisfy the criteria of a GABA analogue (Introduction, section 4); (3) sugar lactones as the nuclei for further manipulation. Thus, the above novel analogues of this neurotransmitter were prepared so that they could be used to elucidate the structure-activity relationships among the synthetic GABA-active compounds. Since the main bulk of this report is on the lactone chemistry, a few brief comments on the studies of this functional group is of obvious relevance.

(5) The chemistry of lactones

Extensive reviews on this subject have appeared in the recent years.[128]

(5.1) Preparation of lactones

Numerous methods have been described for the synthesis of lactones.[128] Only the most well developed procedures will be mentioned here. They are exemplified by the following 4 categories.

(5.1.1) The formation of the lactone moiety by cyclization through the carbon-oxygen linkage

Intramolecular cyclizations of hydroxy acids, hydroxy acid derivatives and related compounds (e.g., oxoacids) to lactones are by far the most commonly used procedures. There are a large number of reagents available for effecting cyclization, for example, N,N'-

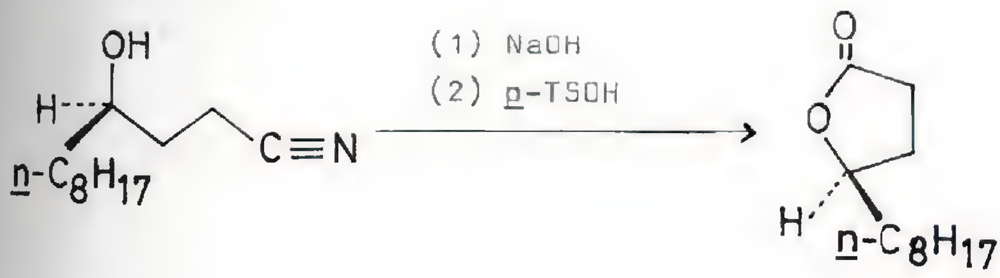
dicyclohexylcarbodiimide, acids (e.g., hydrochloric acid and p-toluenesulphonic acid) and acetic anhydride in various solvent systems.

Solladié has reported the synthesis of the insect pheromone (R)-(+)-γ-n-dodecanolactone by acid catalyzed cyclization[129] (Scheme 1). The hydroxy nitrile (65) is hydrolysed to the corresponding acid, which is then ring closed by acid catalysis to afford the optically active lactone (66).

A series of lactones has also been prepared by the lactonization of γ-halo esters with activated silica gel as catalyst.[130]

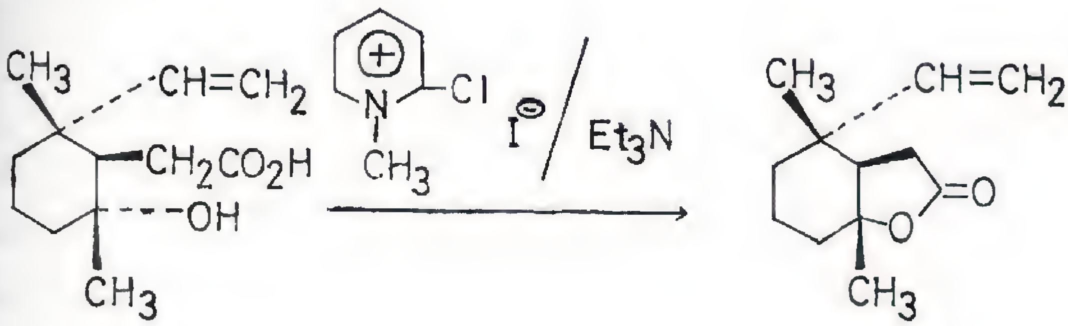
A highly efficient general method for the lactonization of trans-γ- hydroxy acid (67) mediated by 2-chloro-1-methylpyridinium iodide in the presence of triethylamine to the trans-fused bicyclic γ-lactone (68) has been reported by Battiste and coworkers.[131] This procedure can successfully overcome the problem of competitive dehydration of the tertiary hydroxy function.

Unsaturated acids and esters can also be cyclized by self-addition, provided suitable reagents are used, e.g., by acid catalysis[132] (Scheme 3) or by halolactonization (Scheme 4).[133] Chamberlin has reported a stereoselective method for preparing 3-hydroxy-γ-lactones [e.g.,(72)] by iodolactonization under conditions of kinetic control.[133a]



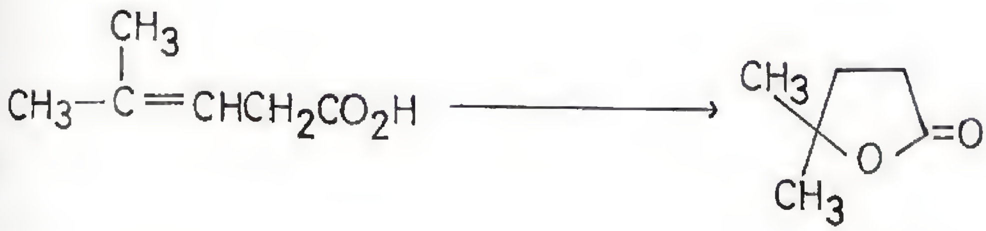
(65) (66)

Scheme 1



(67) (68)

Scheme 2



(69) (70)

Scheme 3

(5.1.2) Lactone synthesis via carbon-carbon bond formation reactions

(A) Intramolecular cyclization reactions

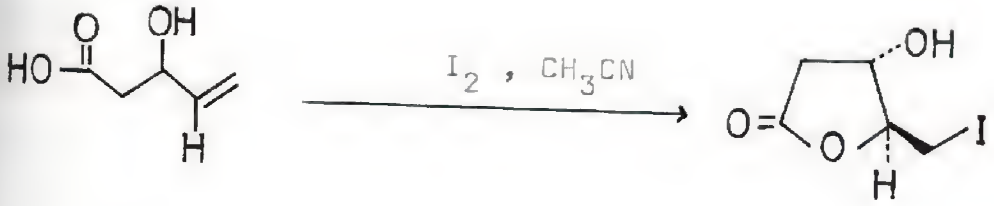
Diels-Alder [4+2] cycloaddition reactions have been applied in the biomimetic synthesis of podophyllum lignans[134] and also as an approach to the pentacyclic skeleton of the yohimboid alkaloids.[135] Thus, as outlined in Scheme 5, the unsaturated ester (73) can be thermolyzed to give a mixture of the cis- and trans-hydroisobenzofurans [135] [(74) and (75)].

[2+2] Cycloaddition can also be used.[136] The hydroxy-γ-butyrolactone (79) has been prepared in good yield by the cycloaddition of α,β-epoxy-aldehyde (76) with the ketene acetal (77), via the intermediate oxetane [136a] (78) (Scheme 6).

(B) By the use of carbanions generated from acetoacetic ester, malonic acid and ester and other acidic methyl or methylene groups

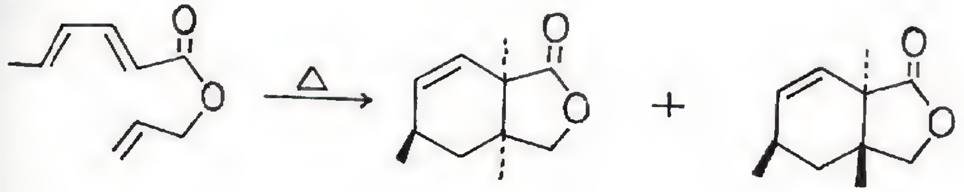
The reaction of the epoxide [e.g.,(80)] with diethyl sodiomalonate[137] in ethanol leads to the lactone ester (82) as a diastereomeric mixture (Scheme 7).[137a]

The anions of the ethyl esters of aliphatic acid[138a] (83) have been reacted with bromoacetaldehyde to give the hydroxy esters (84), which can be hydrolyzed to the lac-



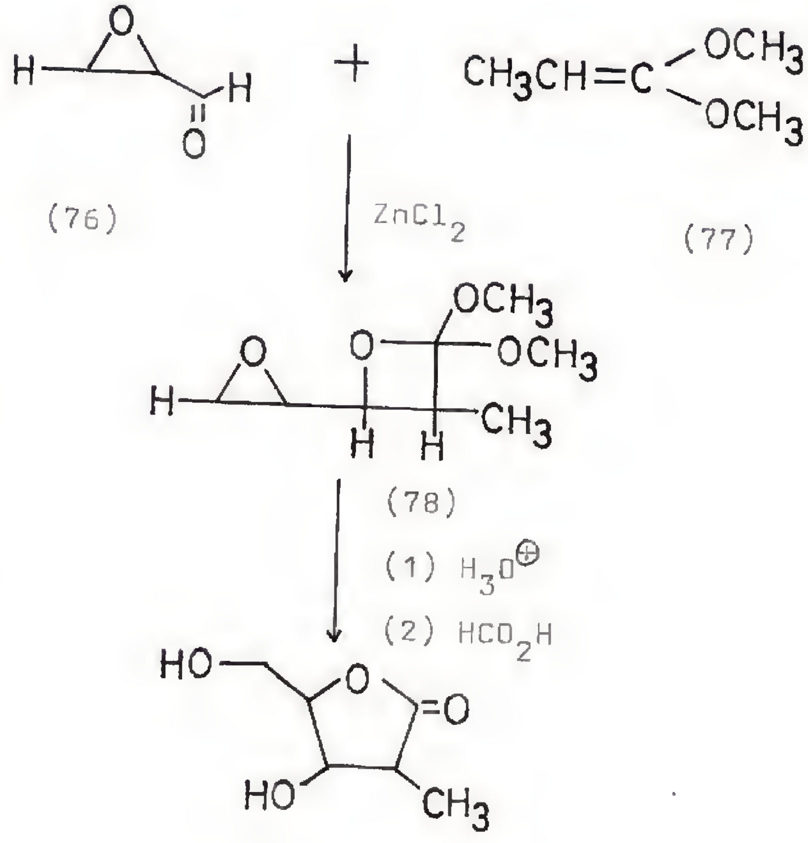
(71) (72)

Scheme 4



(73) (74) (75)

Scheme 5



(76) (77) (78) (79)

Scheme 6

tones (85) (Scheme 8). Similarly, the anion of ethyl 2-phenylthiopropionate[138b] can be generated at -78^{o} with lithio diisopropylamine (LDA) and reacted in THF with the appropriate α-acetoxy aldehyde, e.g., (86), to afford the lactone (88) after work-up (Scheme 9). The use of lithium enolates has also been reported[138c] to effect the cleavage of oxetan rings to yield δ-lactones.

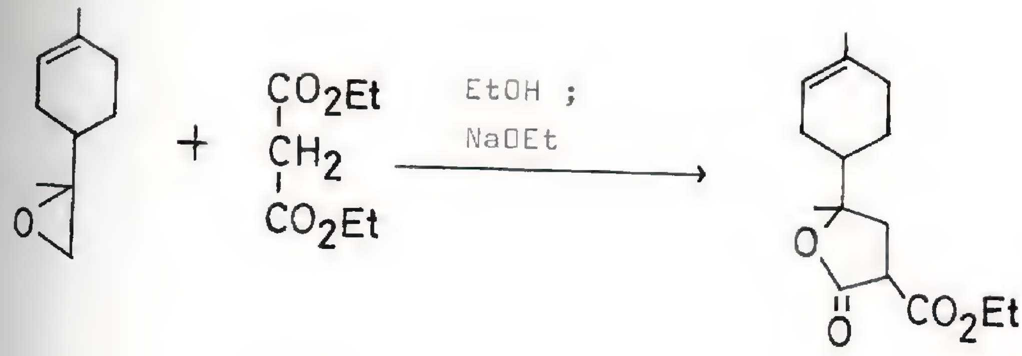
Potential central nervous system agents have been prepared by the reaction of N-phenylbenzamide (89) with the required ketone, in the presence of a strong base (e.g., n-butyllithium) to afford the spirophthalides[138d] (90a and b) (Scheme 10).

(C) The lithio salts of 2-alkyl-2-oxazolines

Synthon chemistry has been exploited by Meyers and Mihelick to produce γ-butyrolactones.[139] Thus, the salt of the masked carboxylic acid (91) can be generated[139] and reacted with allylbromide to give (92), which can be hydrolyzed to afford first the hydroxy acid and hence the unsaturated lactone (93) (Scheme 11).

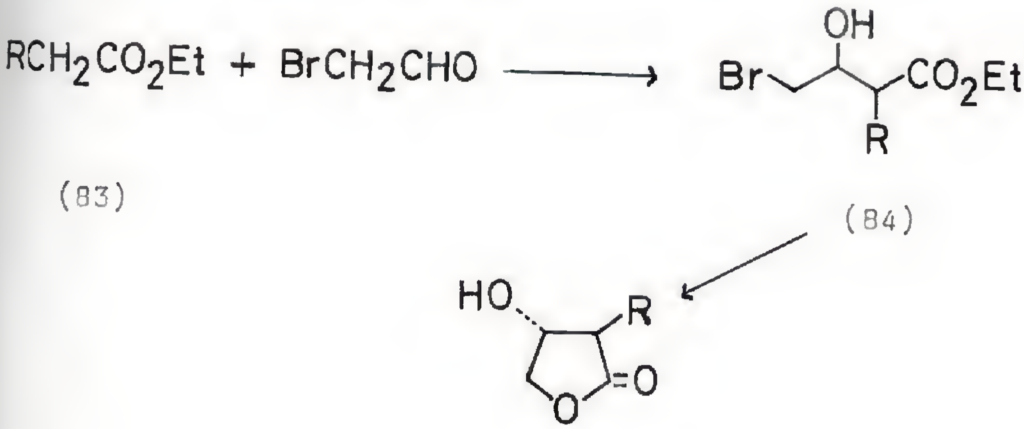
(D) Carbonylation

The simplest way to effect carbonylation is to abstract a proton from a carbon chain and react the resulting carbanion with carbon dioxide. This is what Posner[140a] did in the synthesis of the butenolide (95),



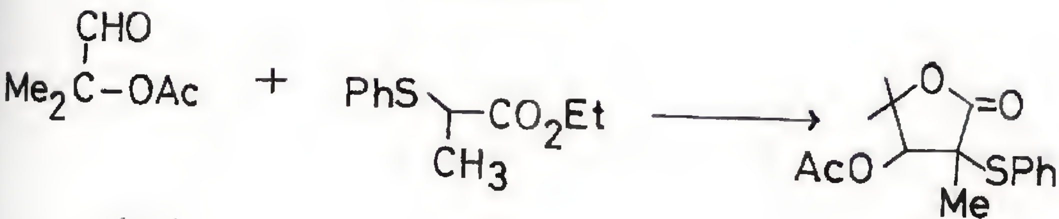
(80) (81) (82)

Scheme 7



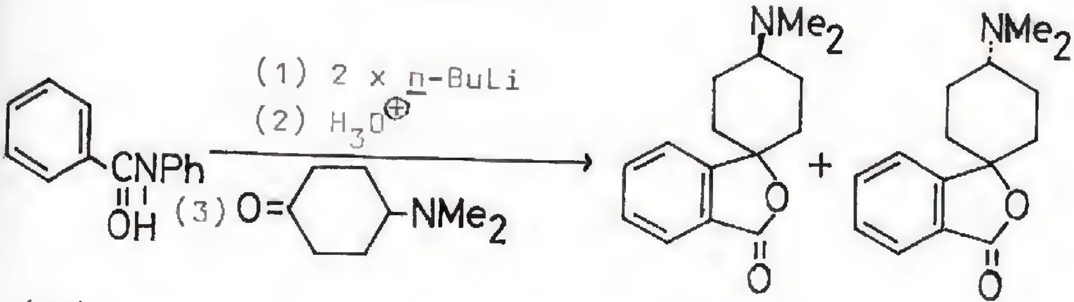
(83) (84) (85)

Scheme 8



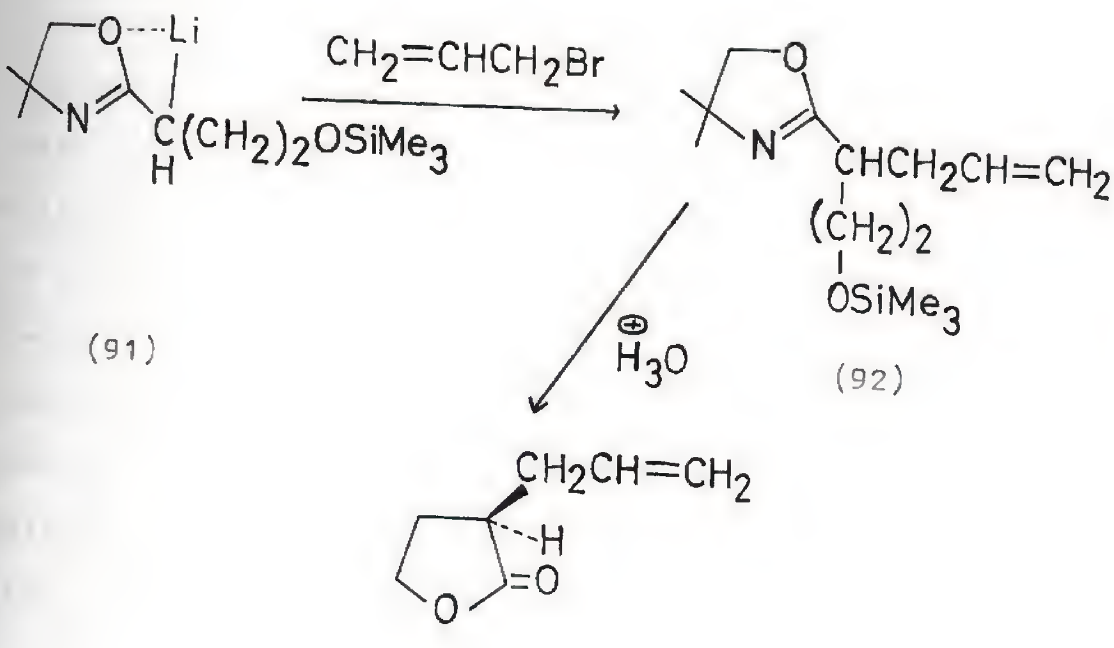
(86) (87) (88)

Scheme 9



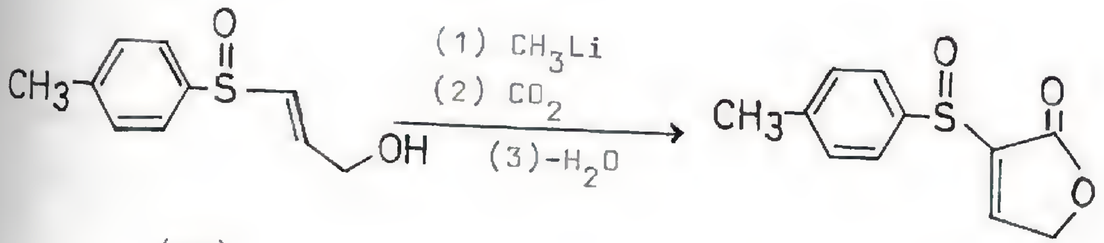
(89) (90a) (90b)

Scheme 10



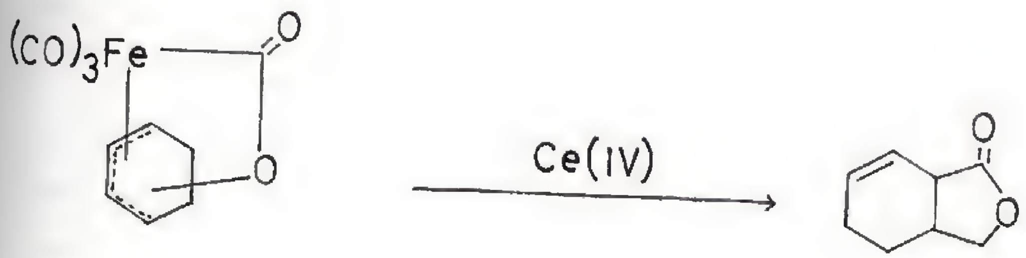
(91) (92) (93)

Scheme 11



(94) (95)

Scheme 12



(96) (97)

Scheme 13

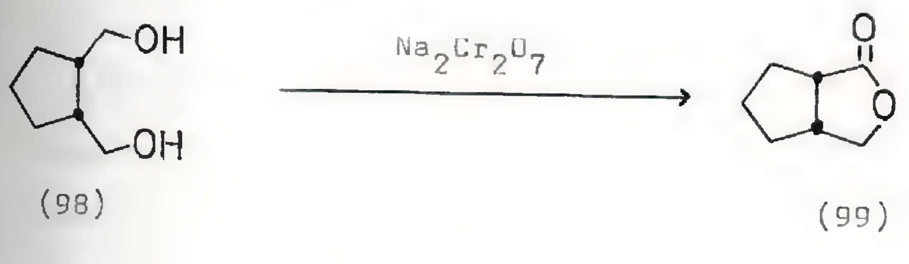
by treating the metallation product of the alkene (94) with carbon dioxide (Scheme 12). This Δ^2-butenolide can be alkylated _via_ a Michael addition reaction to furnish a β-substituted γ- butyrolactone and then the tosylsulphinyl group is removed by Raney nickel reduction to leave the α-position vacant for further transformation.[140a] Interestingly, vinyloxiranes undergo carbonyl insertion when treated with iron pentacarbonyl; oxidation of the resulting complexes [_e.g._, (96)] with a cerium (IV) salt gives the lactone (97) (Scheme 13) as the only isolated product.[140b,c]

(5.1.3) Oxidation of diols, hydroxy aldehydes, and cyclic ketones

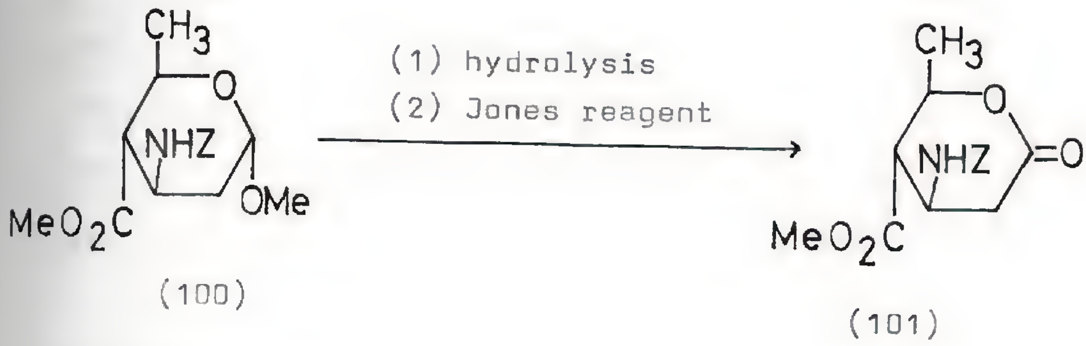
Diols have been oxidized to the corresponding lactones by reagents such as silver carbonate/celite,[141a] sodium bromite[141b] and ruthenium complexes.[141c]

The _cis_-diol (98), which was not oxidized by Sarett's reagent (chromium trioxide-pyridine complex), was oxidized smoothly by sodium dichromate[141d] to give the bicyclic _cis_-lactone (99) in 60% yield (Scheme 14).

Unsubstituted hydroxy aldehydes (_e.g._, 1-unprotected sugars) have been oxidized to lactones by bromine,[142a] sodium dichromate,[142b] or Jones reagent.[142c] In a stereocontrolled synthesis of a chiral thienamycin intermediate[142c] from D-glucose, the methyl glycoside (100) was first selectively hydrolyzed to give the hydroxy aldehyde, and subsequently oxidized to the corresponding lactone (101)

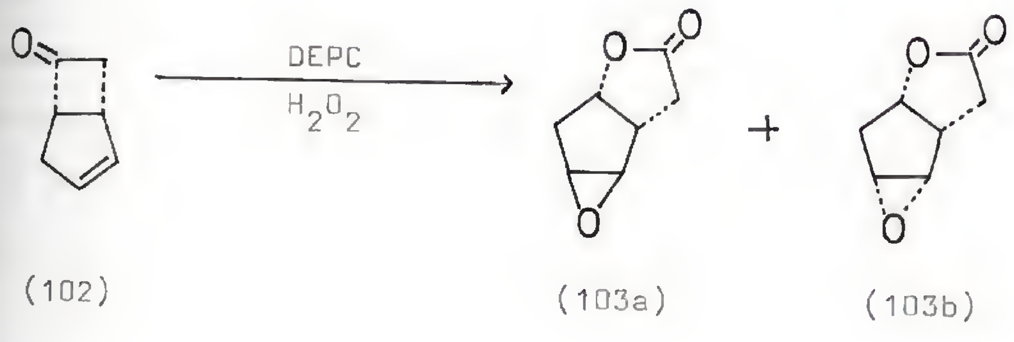


Scheme 14



Z = C(=O)OCH$_2$Ph

Scheme 15



Scheme 16

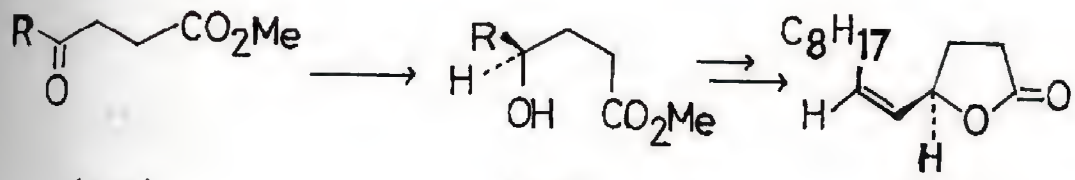
(Scheme 15) by Jones reagent.

The conversion of cyclic ketones (e.g., cyclobutanone) into lactones can usually be accomplished by a Baeyer-Villiger reaction.[143] The usual oxidant for this transformation is a peracid (e.g., meta-chloroperbenzoic acid). Recently, an extremely versatile reagent, diethyl cyanophosphonate (DEPC) has been developed. In combination with hydrogen peroxide,[143a] this mixture oxidized both the olefin and cyclobutanone of (102) to the epoxy lactone (103) as a mixture of isomers (Scheme 16).

(5.1.4) Reduction of anhydrides, esters and acids

γ-Keto-acids and their derivatives can be reduced to the corresponding hydroxy acids or esters, and hence to lactones as the final products. Reducing agents used include sodium borohydride,[144a] lithium aluminium hydride[144b] and potassium tri-S-butylborohydride [144c] (K-Selectride). Selective reduction of oxo-esters and lactonic acids or esters has also been achieved by using borane-methyl sulphide[144d] (BMS) and β-isopinocampheyl-9-borabicyclo[3.3.1]nonane [144e] (Alpine-Borane).

Reduction of γ-keto-ester (104) with Alpine-Borane[144e] proceeds under mild conditions to afford the hydroxy ester (105), in excellent enantiomeric purity, which is then converted to the naturally occur-



(104) (105) (106)

R = $\underline{n}$-$C_8H_{17}C{\equiv}C$—

Scheme 17

ring sex pheromone (106) of the Japanese bettle, Popilla japonica (Scheme 17)

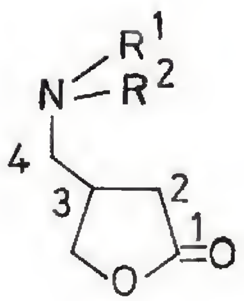
Lactones are potentially valuable intermediates[145] for further chemical manipulation, and they may also provide materials for pharmacological investigations in various areas of medical research.[146] The undoubted interest in the behaviour of amino-substituted butyrolactones as potential neurotransmitters in particular, and the more general importance of γ-lactones in medicinal chemistry provides the basis for the work described in this thesis.

In this dissertation, for the ease of search of compounds and unambiguity in naming them, the Chemical Abstract nonemclature is adopted and used in the experimental section. However, these names are usually very long; for the convenience of writing, trivial and IUPAC (International Union of Pure and Applied Chemistry) names are commonly employed in the other parts of the report.

DISCUSSION

(1) Preparation of β-aminomethyl-γ-butyrolactones (120)

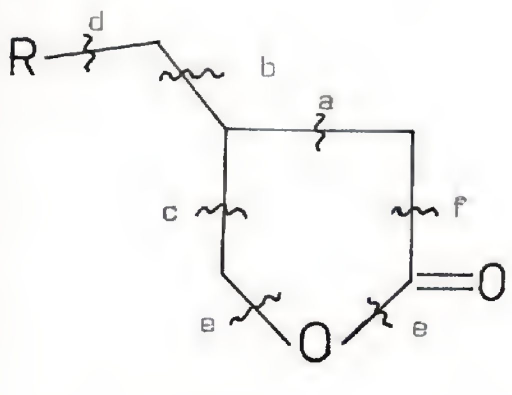
The structure of β-aminomethyl-γ-butyrolactones [(120), see p.54] can fit that of γ-aminobutyric acid [GABA, (1)] (p.16) well, as shown in the diagram of the molecule [(107), see p.50], which has been numbered according to the carbon skeleton of GABA (5) or (6). Due to the near-planarity of the lactone ring,[147] the aminomethyl substituent can only exhibit an extended conformation of GABA (5), which is also similar to that of the relatively rigid structural analogue of GABA, trans-aminocrotonic acid [58a] [(22a), see p.27]. This is observed on examination of the Dreiding models of (107). Since it shows a structural resemblance to GABA while still retaining some essential features of bicuculline [(3), see p.16], i.e., the lactone ring and a non-zwitterionic nature (for a detailed discussion see, Introduction, Section 4.1.1), we have given priority to the synthesis of these compounds, and a major part of the work is devoted to studies of these lactones.



(107)

(1.1) Strategies of synthesis

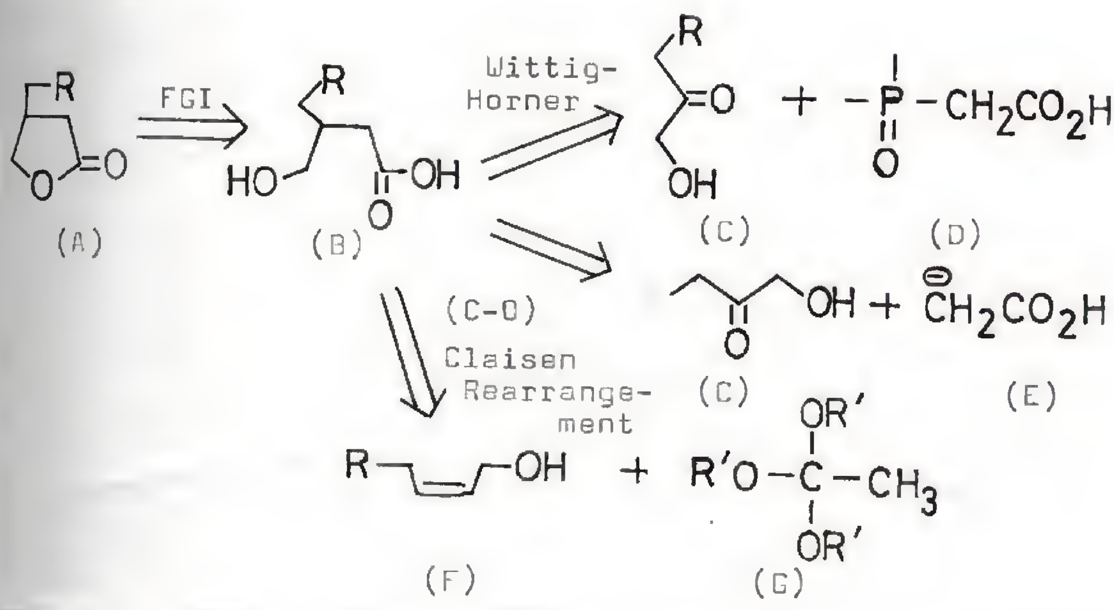
All the possible alternative disconnections[148] of the molecule are shown below.



(A)

The analysis of each of the four carbon-carbon disconnections and of the two carbon-heteroatom disconnections are considered in turn, highlighting the points of linkage.

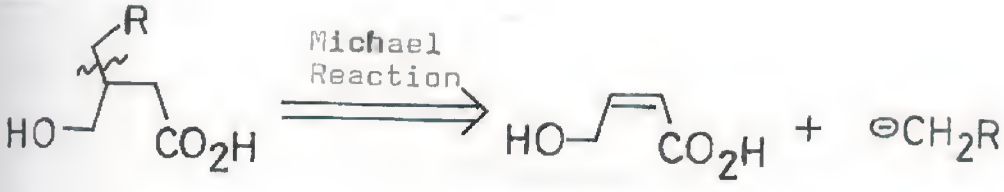
(a)-Disconnection



FGI = functional group interconversion

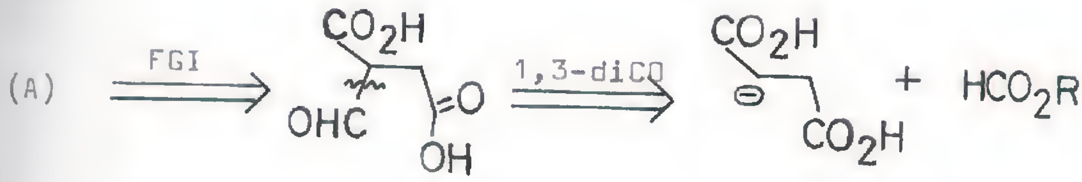
C-O = via carbon-oxygen bond

(b)-Disconnection



(B) (H) (I)

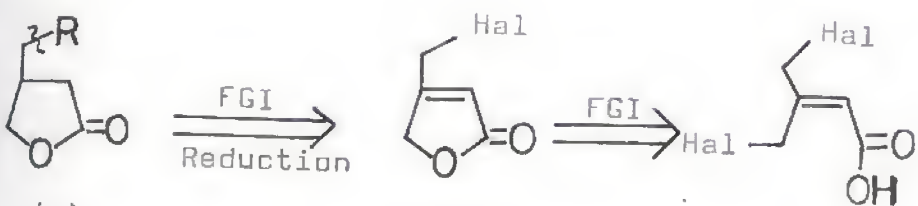
(c)-Disconnection



(J) (K) (L)

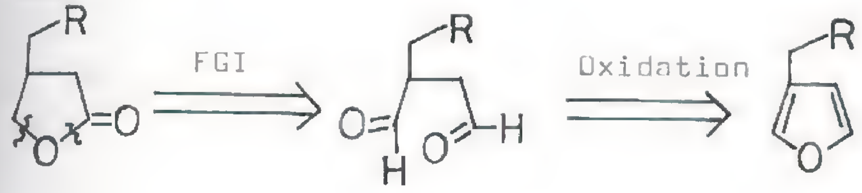
1,3-diCO = 1,3-di-carbonyl formation

(d)-Disconnection



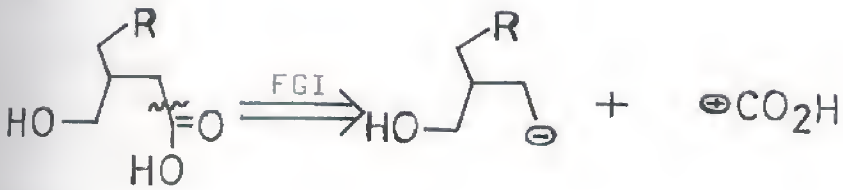
(A) (M) (N)

(e)-Disconnection



(A) (O) (P)

(f)-Disconnection



(B) (Q) (R)

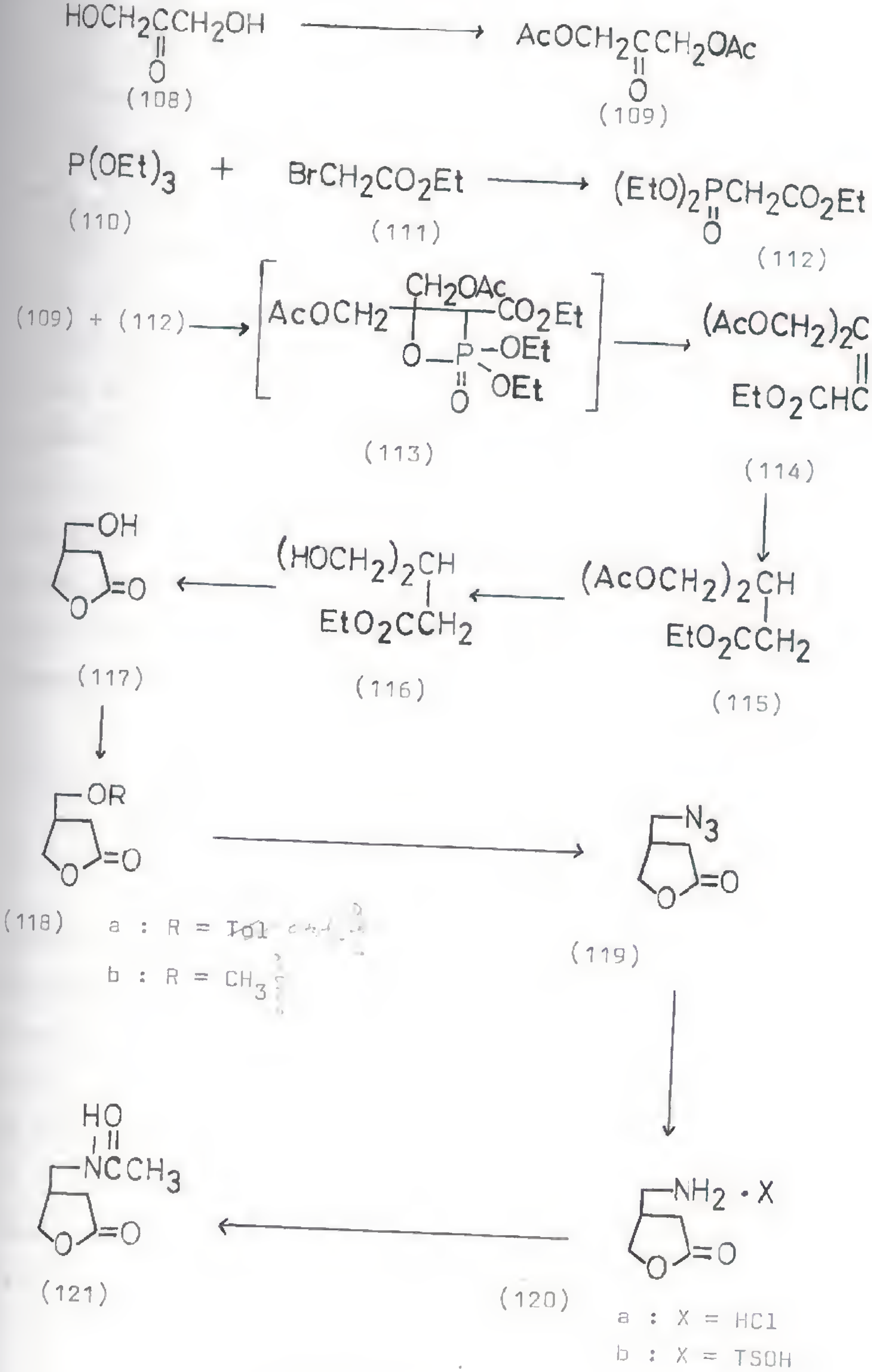
N.B. (f) was the only disconnection which had not been attempted in this work.

(1.2) Synthesis by way of (a)-disconnection

Judging by the analysis, this was the one with most appeal. Approaches to this problem are exemplified as follows.

(1.2.1) Preparation of β-aminomethyl-γ-butyrolactone salts (120) via a Wittig-Horner reaction

The stages involved in the synthesis are depicted in Scheme 18.



(108)
(109)
(110)
(111)
(112)
(113)
(114)
(115)
(116)
(117)
(118)
a : R = Tol
b : R = CH3
(119)
(120)
a : X = HCl
b : X = TSOH
(121)

Scheme 18

(1.2.1.1) Starting materials (109) and (112)

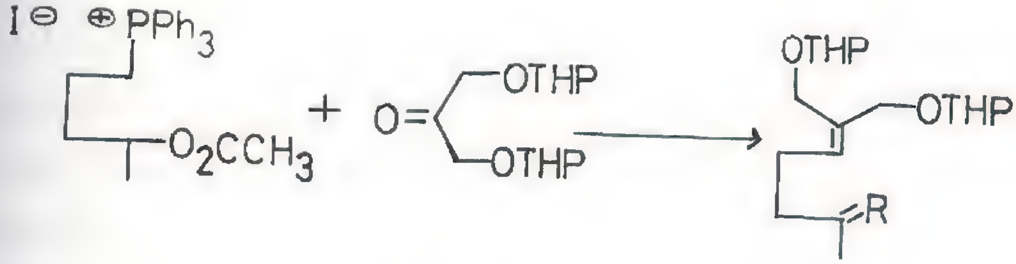
The bis-acetylated compound (109) was prepared by a reported procedure[149] in 81% yield after recrystallization from benzene and petroleum ether 40-60^{o}. It was fortunate to choose the acetate (109) as a direct form of protection instead of functionalizing the ketone group first. In a recent communication, Jones and co-workers have disclosed the blocking of the carbonyl moiety by thioketalization ending in a mixture of compounds.[150] The phosphonate (112), which was required for the Wittig-Horner reaction was obtained as a colourless liquid by the method of Wolinsky and Erickson.[151] In the latter stage of the research, the organophosphorus derivatives (112) was purchased from Aldrich Chemical Company and used without further purification.

(1.2.1.2) Condensation leading to the α,β-unsaturated ester (114)

Phosphonate esters [e.g., (112)] with a second stabilizing group form anions which undergo a Wittig-like reaction with both aldehydes and ketones,[152] known as the Wadsworth-Emmons modification of the Wittig reaction. In general the Wadsworth-Emmons-Horner reagents are more reactive than the corresponding Wittig ylides, due to the fact that the phosphono-groups give less contribution towards the stability of the anions than does the triphenylphosphonio-group.

The olefin (124a) has been prepared from the bis-

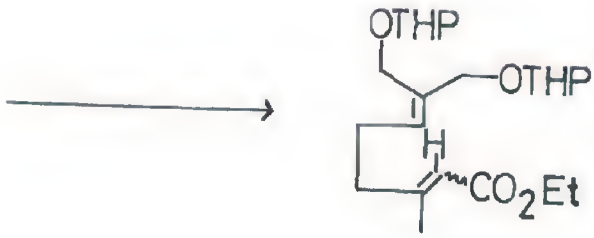
(A)



(122) (123) (124)

a : R = H, OH
b : R = O

(B) (124b) + (112)



(125)

Scheme 19 : (A) and (B)

tetrahydropyranyl protected ketone (123), using excess n-butyllithium as base, as outlined in Scheme19, during the studies on monoterpene glycosides.[152b] The resulting unsaturated alcohol (124a) was further oxidized to the ketone (124b) which underwent a Wittig-Horner reaction, with sodium hydride as base, to furnish the unsaturated ester (125).

The olefination reaction was carried out by generating the anion of (112) *in situ*[151,153] and reacting with the ketone (109). The reaction was monitored by thin layer chromatography (TLC). It was observed that the reaction never went to completion, but stopped after about 60% of

the starting materials were consumed. It was probably due to the formation of the heavy sediment of sodium diethylphosphate. Like the Wittig reaction, the mechanism[152c] involves a four-centre intermediate (113). The product was purified by column chromatography. The structural assignment of the α,β-unsaturated ester (114) was made on the basis of its proton nuclear magnetic resonance spectrum (PMR), carbon-13 nuclear magnetic resonance spectrum (CMR) and also infrared spectroscopy (IR). The PMR spectrum of the alkene (114) shows the methylene protons <u>cis</u> to the olefinic proton are at higher field (δ4.80) than those <u>trans</u> to it, which resonate at δ5.38, attributed to the shielding and deshielding effects of the carbonyl group[154] on the two sets of protons, respectively. Both appear as broad singlets. However, an apparent triplet is observed for the olefinic proton with a coupling constant, <u>J</u>, value of <u>ca</u>. 2 Hz. In fact it may have been an overlap of 2 triplets as a result of allylic couplings with the aforementioned methylene groups (see Spectra Section, Spectrum P-1). However, this anisotropic effect of the carbonyl group is less significant in influencing the carbon chemical shifts[155] of the allylic methylene groups, which give signals at δ61.7 and 63.8, respectively, a difference of only <u>ca</u>. 2 ppm (also see Spectra Section, Spectrum C-1). The structure is further confirmed by a band at 1615 cm^{-1} assigned to the C=C double bond in the IR spectrum.

(1.2.1.3) Hydrogenation of the alkene (114)

α,β-Unsaturated carboxylic esters can be hydrogenated to provide the corresponding saturated esters.[156]

Hydrogenation (H_2-Pd) of the α,β-unsaturated ester [(114), see p. 54] gave the saturated compound (115) in good yield. This is indicated in the PMR spectrum where the olefinic signals disappear, to be replaced by a band of complex signals, δ2.08 to 2.80, which can be attributed to the α-methylene and the methine protons. However, the signals are too complex to be analysed in detail, because of the non-equivalence of the α-methylene protons and the multi-proton environment of the methine proton (Spectrum P-2). Fortunately, due to the symmetrical nature of the branched-chain methylene group ($AcOCH_2$), a strong doublet is seen at δ4.15, showing a coupling of 6 Hz with the adjacent methine proton. The CMR spectrum of (115) is very much simpler and all the required carbon signals can be located (Spectrum C-2).

(1.2.1.4) Deacetylation of the ester (115) and subsequent cyclization to the hydroxy lactone (117) and related reactions

Removal of the acetate protecting group as part of a chemical transformation has been studied.[157] In carbohydrate chemistry, the use of alkoxide to deprotect acetate is a well-known process.[158] Therefore, the diacetate [(115), see p.54] was converted to the diol (116)

by the employment of either sodium ethoxide in ethanol or sodium methoxide in methanol. After the reaction, the resulting sodium acetate was neutralized with an acidic resin (Dowex-50W-X8). The product was obtained after evaporation of the solvent. Analysis of the spectral data revealed that the product was a mixture of the dihydroxy ester (116) and the hydroxy lactone (117), as judged by the diminished integration of the ethyl proton signals and the presence of a lactone carbonyl band in the IR spectrum. This can probably rationalized by the fact that lactonization of the hydroxy ester (116) is possible because of the presence of some acetic acid and the acidic resin.

Without further purification, the mixture was treated with a catalytic amount of p-toluenesulphonic acid in ethanol. The hydroxy lactone (117) was produced quantitatively (as judged by TLC). However, organic solvents (e.g., ethyl acetate) failed to extract the desired product, which stayed in the aqueous layer. It is not unreasonable to believe that this highly polar small molecule may be water-soluble. Thus it was revolved to clean the mixture by column chromatography. However, a small amount of the contaminant (the sulphonic acid) was still present. Therefore, we decided to try using a volatile acid, trifluoroacetic acid (TFA), to effect lactonization, allowing separation by distillation. Thus the dihydroxy ester (116) was cyclized to the hydroxy lactone (117) with 10% aqueous trifluoroacetic acid.

After work-up, the yield of the required compound was quantitative. However, some water could be detected in the product. Even after prolong azeotroping with benzene, using a Dean-Stark apparatus (6 hours), a trace of water was still retained, probably due to the very hygroscopic nature of the hydroxy lactone, which was obtained as a thick oil.

The most characteristic features of this molecule are the very broad OH absorption band at 3450 cm^{-1} and the lactone carbonyl stretching frequency at 1770 cm^{-1} in the infrared spectrum.

In proton nuclear magnetic spectroscopy, coupling between protons on vicinal carbon atoms in rigid systems depends primarily on the dihedral angle, Ø, between the H-C-C' and the C-C'-H' planes.[159] Here the Karplus equation[160] can be applied to predict the coupling constants, _J_, between vicinal protons:

$$\underline{J}\ vic = \underline{J}^{0} \cos^2 \phi - C \quad 0^{\circ} \leq \phi \leq 90^{\circ}$$
$$\underline{J}\ vic = \underline{J}^{180} \cos^2 \phi - C \quad 90^{\circ} \leq \phi \leq 180^{\circ}$$

The analyses of vicinal proton-proton coupling constants in solution have been demonstrated in six-membered rings,[161] (_e.g._, steroids[159]) five-membered rings,[162] lactones[163] and four-membered rings.[164]

Due to the flexible nature of the γ-butyrolactones, the conformation is not fixed and the vicinal couplings

of the protons will depend on the dihedral angle, Ø.[163] In the 60 MHz or some 100MHz spectra, complex peak patterns for the protons due to second order coupling can be observed. Only the hydroxy-methyl group, gives a simple pattern, appearing as a doublet at δ3.62, with a, coupling constant, J value of 6 Hz (Spectrum P-3). As in the other compounds reported, the CMR spectrum reveals all the carbon atoms distinctively (Spectrum C-3). The assignment of the carbon atoms in the lactone molecule, 1-4, is as follows.

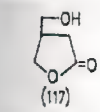
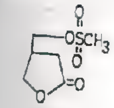
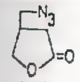
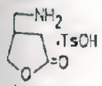
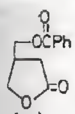
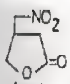
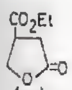
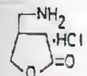
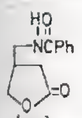
$$\begin{array}{l} \qquad\quad {}^{1'}CH_2 \\ \quad {}^{4}\qquad |\,{}^{3}\ \ {}^{2}\ \ {}^{1} \\ -O-CH_2CHCH_2CO- \end{array}$$

The CMR spectral parameters of some β-substituted γ-butyrolactones are listed in Table 3. The main characteristic signal resonates at δ62.1 which belongs to the hydroxymethyl carbon atom.

Cyclization of polyhydroxy acids, esters or nitriles to the corresponding hydroxy lactones have been reported very frequently.[165-170]

Because of the success we enjoyed with the saturated acetate (115) and also because we wanted to explore the chemistry of the corresponding unsaturated lactone, cyclization directly from the unsaturated ester (114) was attempted. The use of sodium hydroxide according to van Tamelen[171] led to decomposition, only an

Table 3 CMR assignments of some β-substituted γ-butyrolactones (at 15 MHz)

Compound	Solvent	C-1	C-2	C-3	C-4	C-1'	Other Carbons
 (117)	D_2O	181.5	36.1	30.5	71.85	62.1	
 (118b)	$CDCl_3$	175.7	34.5	30.2	69.4	68.7	37.3
 (119)	$CDCl_3$	175.9	34.7	31.3	70.1	52.5	
 (120b)	D_2O + 1,4-Dioxane	180.6	33.9	32.6	72.07	42.9	21.1;126.1;130.2; 140.5and 143.2
 (169)	$CDCl_3$	177.14	39.58	33.98	72.33	117.44	135.80
 (173)	$CDCl_3$	176.42	34.50	31.11	70.37	65.10	128.7; 130.27 and 133.52; 166.40
 (182)	$CDCl_3$	175.19	33.59	31.57	70.25	76.30	
 (194)	$CDCl_3$	176.4	40.1	30.9	69.2	171.5	14.1 and 62.0
 (120a)	D_2O + 1,4-Dioxane	180.98	34.11	32.81	72.33	41.79	
 (183)	$CDCl_3$	177.79	35.67	32.16	71.54	41.73	127.4; 128.77; 131.90; 134.30 & 168.94

acetate signal could be seen in the ^{1}H-NMR spectrum of the total reaction mixture. Similarly, treatment with acids (p-toluenesulphonic acid, aqueous trifluoroacetic acid and hydrogen bromide in acetic acid[172]) resulted in decomposition or formation of only a small amount of the impure product, judging by the NMR spectra.

(1.2.1.5) Sulphonation

Sulphonic acid esters [e.g., (118)] (p.54) are very versatile intermediates in synthetic chemistry. They can be used in displacement reactions with carbon nucleophiles (e.g., Grignard reagents[173]), iodide[174] and azide ion.[175]

The conversion of primary alcohols to the corresponding sulphonates can be achieved using various base-solvent combinations. Generally speaking, primary sulphonic acid esters are more readily prepared than secondary esters (for reviews on sulphonic esters of carbohydrates, see Ball and Parrish[176a,b] and also Harrison and Harrison[176c]).

Tosylation was attempted according to the procedure of Wintersteiner.[177] However, only a trace of impure product (118a) was isolated. This is probably due to the high reactivity of the resulting ester which readily decomposed. Nevertheless, the mesylate (118b) could be prepared using either pyridine as solvent and

base[178] or triethylamine in tetrahydrofuran. The former method gave an isolated yield of only 74%, which was still contaminated with pyridine. Some product was throught to be lost during the aqueous work-up, because of the solubility of the lactone (118b) in water. Thus the latter method was preferred, since the ammonium sulphonate produced was insoluble in the solvent and could be removed by filtration, rendering aqueous washing unnecessary. The yield of (118b) by this process was almost quantitative. Chromatographic purification led to a much lower yield, with no improvement in purity. The mesylate was usually used in the next stage without further purification.

The IR spectrum of compound (118b) shows the absence of the strong hydroxy band of the starting material at ca. 3450 cm^{-1}. Moreover, in the PMR spectrum, the incorporation of the sulphonyl group provides a shift of the exocyclic methylene protons from δ3.62 of the hydroxymethyl compound (117) to a lower field of δ4.39, still a doublet with a coupling constant of 6 Hz. The CMR spectral characteristics of the compound (118b) are presented in Table 3 (p.62).

(1.2.1.6) Azidolysis and amine reactions

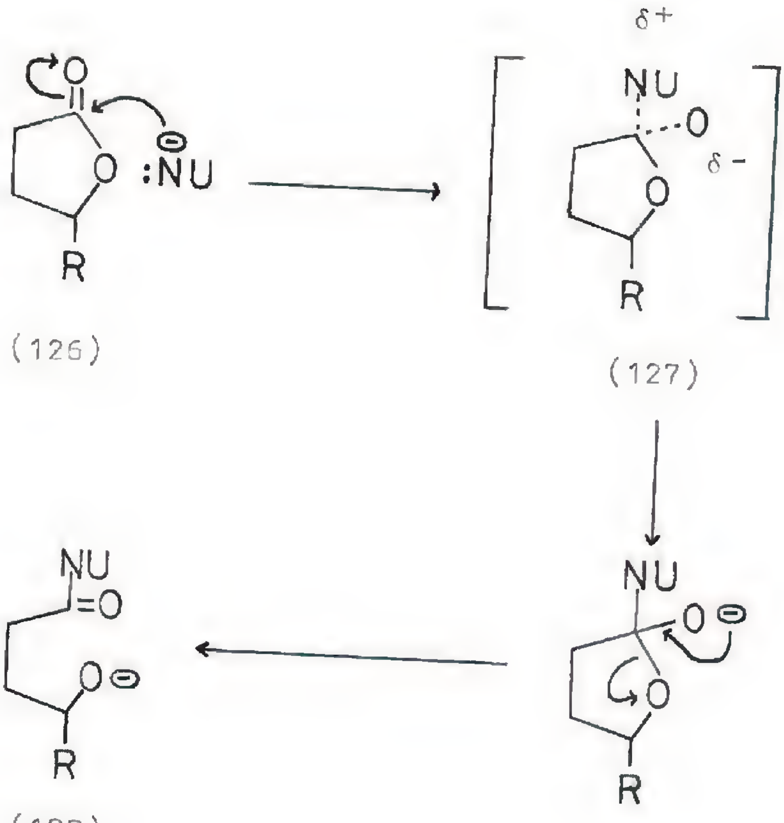
Preparation of azides by nucleophilic displacement of sulphonate with sodium azide is a very useful process.[175,179] It has been employed, for example,

in the synthesis of sugar azides.[180] These azides are widely utilized in the synthesis of amino sugars.

According to the hard soft acid bases (HSAB) theory,[181] soft nucleophiles are predicted to show a preference for attack on the alkyl-oxygen bond (soft-soft interaction) of γ-lactones rather than the carbonyl carbon (soft-hard interaction) and vice versa for hard nucleophiles. These reactions are illustrated by the cleavage of β- and γ-lactones.

As expected, the hard acyl carbon is more susceptible to nucleophilic attack with hard bases[181] (such as hydroxide, alkoxide and ammonia). The reaction proceeds by two steps, with the intermediate formation of a tetrahedral compound (128) (Scheme 20).

The ring opening of lactones through alkyl-oxygen bond fission has been studied with selenium[182] and sulphur[183] nucleophiles (see Scheme 21). Soft bases, including cyanide,[184] chloride[185] and salts of nitrogen-heterocycles[186] have been used to prepare useful intermediates; for example, jasmonoids[182b] (135) (Scheme 22), the cyanopropiolate[184] (136)→(137) (Scheme 23), pyrethroid acids[185a] (138)→(140) (Scheme 24) and the antiviral compound, eritadenine [186a] (141)→(143) (Scheme 25). Similarly, γ-lactones alkylate[147] rather than acylate aromatic compounds in the Friedel-Crafts reaction (Scheme 26). This may be explained in terms



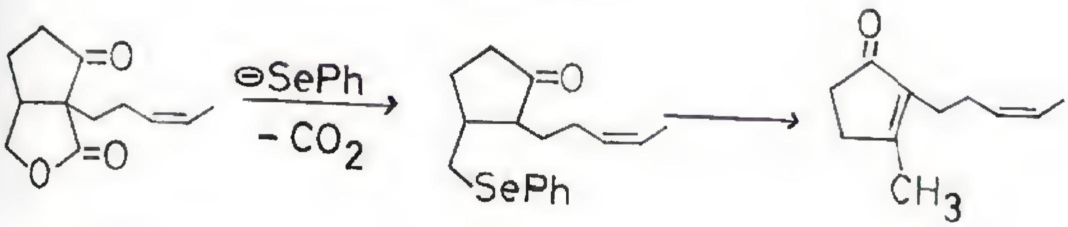
(126) (127) (128) (129)

Scheme 20

(130) (131) (132)

X = Cl, CN, I and SR

Scheme 21

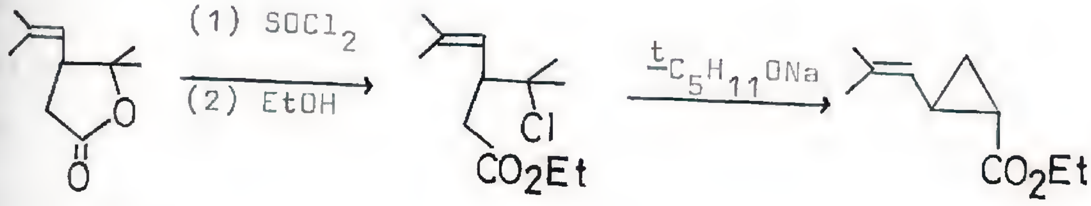


(133) (134) (135)

Scheme 22

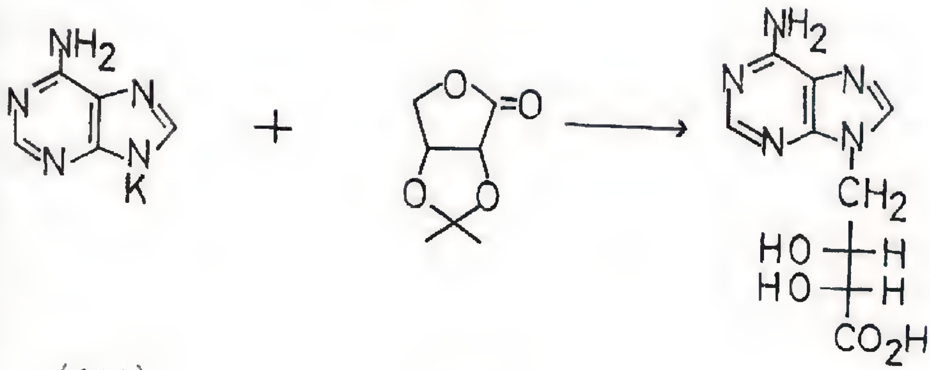
(136) (137)

Scheme 23



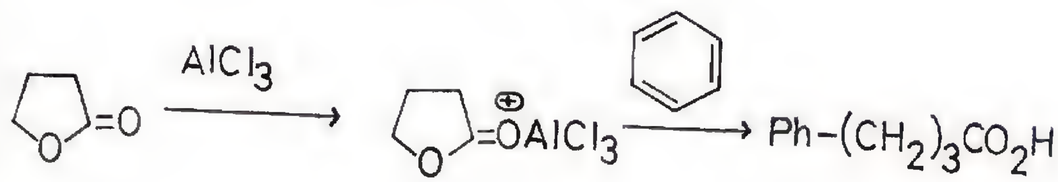
(138) (139) (140)

Scheme 24



(141) (142) (143)

Scheme 25



(144) (145) (146)

Scheme 26

of the hardness of the Lewis acid, $RC{=}O^+$ (145). Since benzene is a soft base[181] and acts as a nucleophile,[187] the soft-soft alkyl-oxygen bond thus preferred for attack and this results in the formation of the acid (146).

For a lactonic sulphonate [e.g., (118b)], using the HSAB principle,[181] there are three sites for which nucleophilic attack is possible. It is known that the soft azide ion can open the ring of a β-propiolactone or γ-butyrolactone at the soft centre (C-OR) leading to the corresponding 3-azidopropanoic acid or 4-azidobutanoic acid.[188] However, in molecules containing sulphonate or halide groups as well as a lactone ring, the controlling factor is the hardness of the leaving group.[181] The carbon attached to a sulphonic acid ester, for instance, becomes the softest centre of the molecule, with the best leaving group attached. Thus soft nucleophiles will prefer to attack the esterified carbon and the sulphonate is substituted.

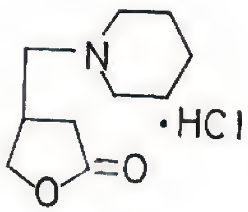
Reaction of the mesylate [(118b), see p.54] with sodium azide in N,N-dimethylformamide for 2 hours at room temperature gave 25% of the desired product (119). The displacement reaction proceeded to completion on heating the reaction mixture in a boiling water-bath for one hour. It proved difficult to remove all the solvent without a substantial loss of product because of the miscibility of the lactone with water. Thus an alternative solvent system was sought. After several trials, a mixture

of acetone and water was found to be satisfactory. It was necessary to reflux the clear reaction mixture for 10 hours for complete reaction. The progress of these reactions were conveniently followed by either IR or NMR spectroscopy. The product and reactant showed very similar behaviour on TLC [Rf values 0.55 and 0.65 (ethyl acetate), for the mesylate (118b) and azide (119), respectively] making TLC unreliable on its own. Unlike the mesylate, the azide could be purified by column chromatography in 73% yield. However, there was still a trace of methanesulphonic acid contaminating the product.

The IR spectrum of the azide (119) shows a strong azide absorption at 2100 cm^{-1} which is as strong as the lactone carbonyl signal at 1775 cm^{-1}. Chemical shifts of the azidomethyl protons in the PMR spectrum is centred at $\delta 3.5$ as a doublet, with a coupling constant, _J_ value, of 6 Hz. The other protons appear as 2 bands of multiplets located at _ca_. $\delta 2.7$ and $\delta 4.5$ (Spectrum P-4). The CMR measurements of the compound (Spectrum C-4) can be found in Table 3 (p.62). The most noticeable change is that of C-1' carbon which shifts from 68.7 to 52.5 after the nitrogen link is formed.

With the sulphonate (118b) in hand, attempts were made to react this compound with amines (including dimethylamine, triethylamine and piperidine) in ethanol. The progress of the displacement was monitored by with-

drawal of aliquots of samples and judged by the disappearance of the diagnostic exocyclic methylene protons at δ4.39 and the emergence of the doublet at higher field, δ3.7, in the PMR spectra. Products were usually obtained as gummy solids. There were signals corresponding to the presence of some of the amine salts [e.g., (147)]. Nontheless, after numerous trials in purifying the products, they were still not pure enough to give



(147)

satisfactory analytical data (some success was reported on a different isomer (246b) [see Discussion, Section (2.2.1.4) prepared by the same method] (see p.124).

Substitutions of the bromolactone (148) by amines were described in 1951, by Brochmann-Hanssen,[102b] as a means of making pilocarpine analogues (148)→(149) (Scheme 27).

(148) (149)

Scheme 27

(1.2.1.7) Hydrogenolysis of the azide (119)

Some hydroxy amino acids are physiologically active compounds,[189] *e.g.*, toxins isolated from mushrooms.[133c,190] Recently, the γ-hydroxymethyl-GABA (26) has been prepared[85] and tested as a GABA analogue (see Table 2) (p.21).

Many chemical methods for the reduction of azides to amines have been reported in the literature[191] (including, *e.g.*, aluminium amalgam, chromous chloride, lithium aluminium hydride, sodium borohydride, sodium sulphide and hydrazine): several of these could be discounted as useful in the present context, since strongly basic conditions were required and such conditions would result in breaking the lactone ring. Nor would it be ideal to carry out the reaction under neutral conditions. Of the various methods available, the use of stannous chloride[192a] together with dilute hydrochloric acid looks attractive.[192b] However, the separation of the inorganic salts from the target molecule, which is itself a potentially water soluble ammonium chloride [*e.g.*, (120)], may impose difficulties. On the other hand, the way to circumvent this problem is to reduce the azide by catalytic hydrogenation in an acidic medium. The work-up conveniently requires a simple filtration and evaporation. Thus, the azide [(119), see p.54] was hydrogenated with 10% palladium-on-charcoal in the presence of aqueous hydrochloric acid or *p*-toluenesulphonic acid in a large vessel [*ca.* 3 times the volume of solvent (*e.g.*, ethanol), so

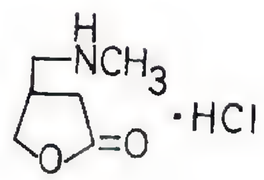
that the nitrogen produced would not depress the volume of the hydrogen pressure]. Usually, the reservoir was evacuated after a certain period and then refilled with fresh hydrogen. The yields of the target compounds were quantitative as the ammonium salts (120). In the case of the hydrochloride salt, only a gum was obtained. However, the gummy tosylate (120b) crystallized gradually on storage.

The IR spectra of the salts (120) are consistent with the assignment. The azide signal has vanished and is replaced by the broad ammonium absorption band, while the lactone carbonyl stretching frequency is still intact. The CMR spectral data are recorded in Table 3 (p.62).

Attempts were made to prepare N-substituted amino compounds [e.g., (150), see p.73] by reductive alkylation.[191a] The hydrogenation of the azide (119) in the presence of formalin was expected to provide either the mono- or dimethylamino compound [e.g., (150)] via the imine, which forms by condensation of the resulting amine with the aldehyde. The imine is then reduced to the monoalkylated amine which can be alkylated further by the same sequence. However, an inseparable mixture was obtained, which showed absorption peaks assigned to lactone in the IR spectrum, and some required proton signals in its NMR spectrum. Because of the difficulties encountered in the purification of these

products, no further work was done on these mixtures.

In order to characterize the amino lactone (120), the corresponding N-acetyated compound (121)(p.54) was prepared. In a preliminary reaction, the hydrochloride (120a) was suspended in acetic anhydride and then triethylamine was added to neutralize the salt, so that the free amine could initiate the attack on the anhydride to



(150)

give the acetamide (121). However, the isolated yield was low (27%). Thus a Schotton-Baumann-type procedure[193] was followed in the latter runs. The yield was since improved. On the other hand, the use of sodium acetate as catalyst failed to produce any reaction.

The most diagnostic features are the amide signals at 1640 and 1540 cm^{-1} in the IR spectrum and the 3-proton singlet of the acetamide (121) in the PMR spectrum. The CMR spectrum of the compound also shows the signals belong to the acetamide at δ20.4 (methyl carbon) and 169.1 (amide carbonyl carbon atom).

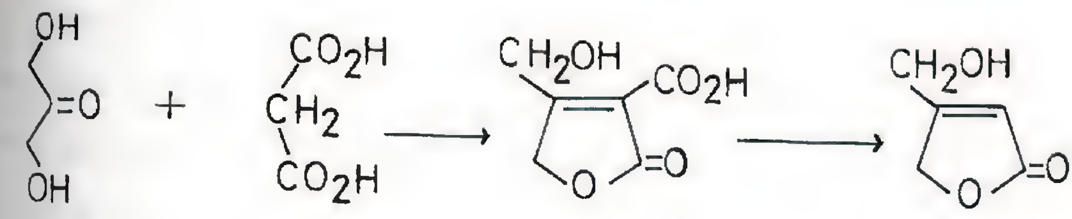
(1.2.2) Attempted preparation of (152) by a Knoevenagel-Cope reaction

As outlined in the retrosynthesis (Discussion, Section 1.1), the hydroxy lactone (117) (see, p.54) can also be made via the synthetic equivalent or synthon for $\ominus CH_2CO_2H$. This is to use either malonic acid or diethyl malonate as the starting material.[148]

The condensation of aldehydes or ketones, usually not containing an α hydrogen, with compounds of the form $Z\text{-}CH_2\text{-}Z'$ or $Z\text{-}CHR\text{-}Z'$ is usually called the Knoevenagel reaction.[194] For doubly activated compounds, it is illustrated by the synthesis of the butenolide [e.g., (151)] (Scheme 28). Various bases have been employed, such as triethylamine, piperidine, sodium hydroxide and potassium amide. However, when pyridine is used, the reaction is known as the Doebner modification of the Knoevenagel reaction.

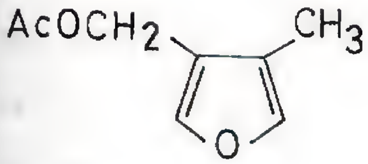
Utilization of ammonium and amine acetate as catalyst introduced by Cope[195] is reckoned as a significant modification of the Knoevenagel reaction. The usual procedure is to do the reaction with a catalyst in some water-immiscible solvent such as benzene, chloroform or toluene, boiling the mixture and resultant water is separated using a Dean-Stark apparatus.

The proposed construction of the butenolide (151) is shown in Scheme 28. Thus a mixture of dihydroxyacetone

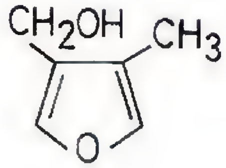


(108) (151) (152)

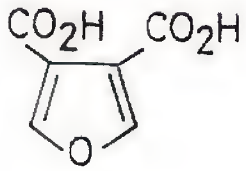
Scheme 28



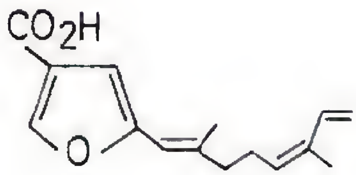
(153)



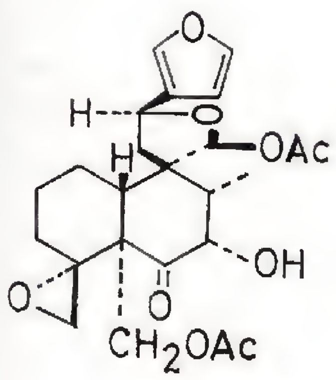
(154)



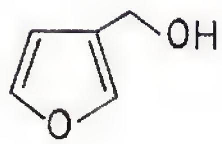
(155)



(156)



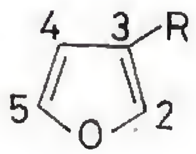
(157)



(158)

(108), malonic acid and ammonium acetate was suspended in benzene and heated with a Dean-Stark set-up attached[195b] and two products obtained (see Experimental Section). The spectra of these components were not consistent with their expected structures (151) or (152). Their IR spectra are very similar to each other except that the spot running slower on TLC has a broad OH band, while the faster running spot has a strong carbonyl signal at 1720 cm^{-1}, most likely to be an ester. In the NMR spectra, the only difference is a 3-proton signal at δ2.15, which is similar to an acetyl singlet, in the component faster on TLC and a deuteratable signal at δ4.3 in the other. Both also have aromatic methyl signals. The low field signals of the compounds are very much like those of the 3,4-disubstituted furans.[196] The C-13 NMR spectra confirm these predictions.[197] Comparisons of the PMR and CMR assignments of some furans, together with those of the two products, are presented in Table 4. Therefore, the compounds are assigned as 3-methyl-4-[(acetoxy) methyl] furan [(153), faster spot] and 3-methyl-4-(hydroxymethyl) furan [(154), slower spot] (Spectra P-5 and C-5), according to the above spectroscopic evidence. The spectra of 3-hydroxymethylfuran [(158), Spectra P-6 and C-6] are also presented for identification purposes.

Table 4A : PMR assignments of some furan ring protons



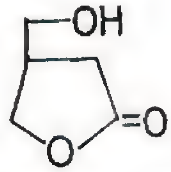
Compounds	C-2H	C-3H	C-4H	C-5H	References
153	8.22	-	-	8.8	this thesis
154	8.59	-	-	8.72	this thesis (Spectrum P-5)
155	8.5	-	-	8.5	196
156	7.92	-	6.4	-	197a
157	7.36	-	6.37	7.36	197b
158	7.4	-	6.43	7.4	Spectrum P-6

Table 4B : CMR assignments of some furan carbon atoms

Compounds	C-2	C-3	C-4	C-5	References
153	143.03	148.3	153.8	144.3	this thesis
154	142.1	152.0	152.9	143.4	this thesis (Spectrum C-5)
156	133.43	119.92	106.67	154.99	197a
157	143.4	127.6	108.5	139.3	197b
158	143.68	125.52	110.15	140.23	Spectrum C-6

(153) and (154) are possibly furan derivatives, but the evidence given above is quite inadequate to allow more specific characterization.

(1.2.3) Synthesis of β-hydroxymethyl-γ-butyrolactone (117) via Claisen rearrangement



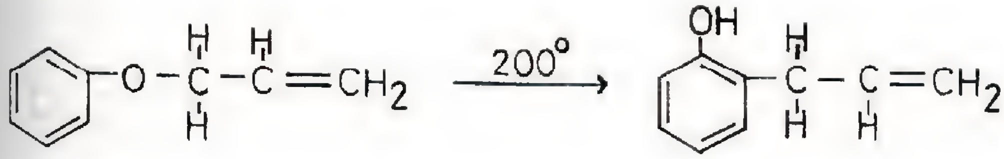
(117)

(1.2.3.1) Preparation of β-vinyl-γ-butyrolactone (169)

The Claisen rearrangement originally referred to the reaction of an allyl arylether, which on heating rearranges to give an O-allylphenol[198] (e.g., Scheme 29).

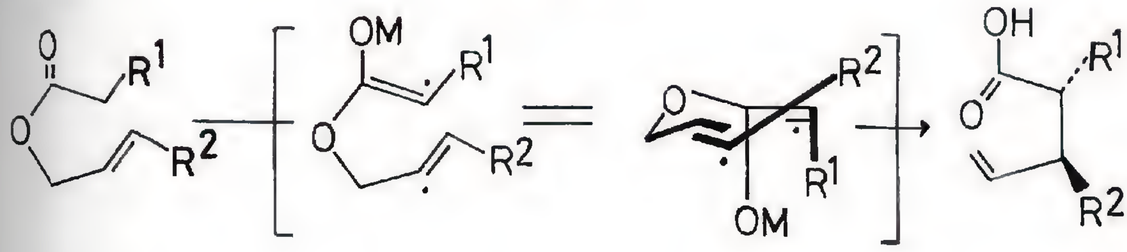
A variant of this reaction, the Ireland-Claisen rearrangement, involves a [3,3] sigmatropic rearrangement of enolates (or trialkylsilyl ketene acetals) derived from esters of allylic alcohol[199] providing a γ,δ-unsaturated acid. This conversion is under diastereoselective control[199e] (see Scheme 30).

Yet another variant is the orthoester-Claisen rearrangement[200] (e.g., Scheme 31). We had envisaged that the application of this rearrangement could lead us to an intermediate which could be employed to produce the important hydroxy lactone (117). The method reported by Mori[201a] was used by us to prepare β-vinyl-γ-butyrolactone (169). This required the condensation of 2-alkene-1,4-diols [e.g., (165)] with an orthocarboxylic ester, in the presence of a catalyst, hydroquinone



(159) (160)

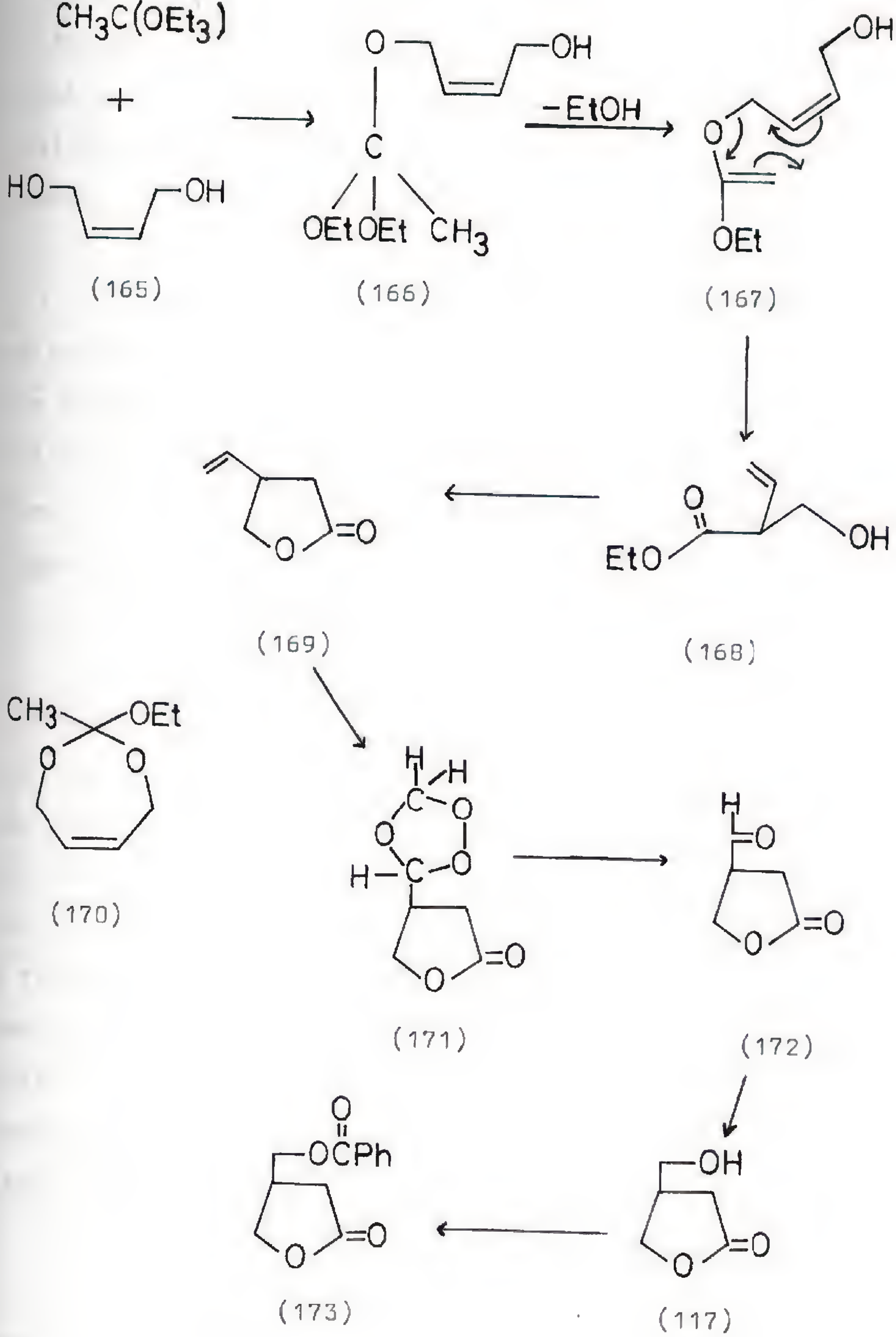
Scheme 29



(161) (162) (163) (164)

Scheme 30

(Scheme 31). The 2-carbon unit is provided by triethyl orthoacetate. The mixture was heated under reflux until all the diol (165) was consumed, when the excess orthoester and product ethanol were distilled off at atmospheric pressure. The cyclic orthoester (170) was obtained by distillation under reduced pressure, in 43% yield. However, in our hands, it was not possible to remove the desired product from the residual hydroquinone by distillation. The tarry residue was investigated by IR and PMR analysis. This revealed that the product was the acyclic hydroxy ester (168). Apparently, the hydroquinone did not effect the cyclization under these circumstances. Therefore, the crude mixture was converted to the lactone (169) by treatment with trifluoroacetic acid. The residue, after evaporation of the solvent, was washed with sodium bicarbonate solution and then water, in an attempt to remove some of the hydroquinone,


CH3C(OEt3)
+
HO
OH
OEt OEt CH3
-EtOH
OEt
(165)
(166)
(167)
EtO
(168)
(169)
CH3
OEt
(170)
(171)
(172)
(117)
OCPh
(173)

Scheme 31

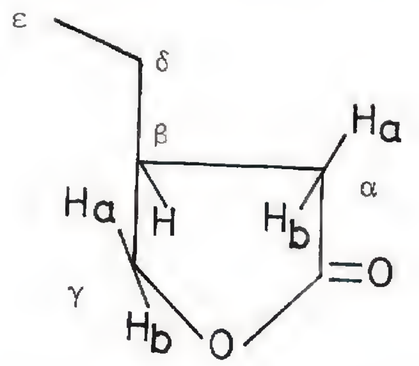
but in vain. (Phenols are by no means as acidic as carboxylic acid and do not react with bicarbonate ion[202]). Purification was achieved by column chromatography. The target β-vinyl-γ-lactone (169) was obtained in 11% yield, still however contaminated by a small amount of hydroquinone, judging by the NMR spectrum.

It is known that the _trans_-2-butene-1,4-diol can achieve a better conversion than the _cis_-isomer[201a] (see mechanism). As stated before, it was for the availability reason that the _cis_-compound (165) was chosen. An 89% yield has been claimed by using the _trans_-isomer.[201a]

The mechanism of the reaction is illustrated in Scheme 31 (see p.80). The acid catalyzed transesterification results in the formation of a new ether. In case of ditransesterification the cyclic orthoester (170) will be obtained. Because of the stereochemistry of the diol (165), which being _cis_, will be more prone to undergo further reaction to produce the novel acetal (170). Removal of one molecule of ethanol provides a vinyl ether or ketene acetal (167) which undergoes Claisen rearrangement as predicted to furnish the hydroxy ester (168) (Scheme 31).

The IR spectrum of the vinyl lactone (169) shows a lactone carbonyl signal at 1740 cm^{-1} and a double bond peak at 1622 cm^{-1}. The protons of the

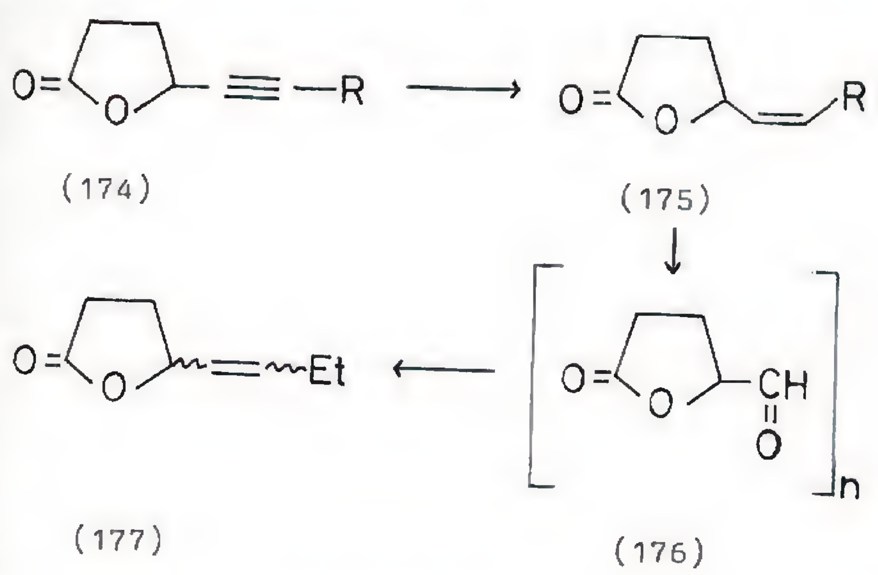
γ-lactone assigned are in Greek alphabets:



In the PMR spectrum (200 MHz) the α protons appear as 2 sets of doublet of doublets (or doublet of AB quartets) centred at δ2.48 and 2.7, with coupling constants $\underline{J}_{(\alpha,\beta)}$ = 8 (for both $H_{\alpha a}$, and $H_{\alpha b}$). The methine proton is at δ3.22 as a band of multiplet. However, the γ methylene protons become two groups of distorted doublet of doublets (or doublet of AB quartets) at δ4.03 and 4.46, still with coupling constants $\underline{J}_{(\beta,\gamma)}$ = 8 (for both $H_{\gamma a}$ and $H_{\gamma b}$). Due to second order patterns, the 3 olefinic protons show multiplets at δ5.1-5.28 (see Table 5 and Spectrum P-7). The CMR measurements are listed in Table 3 (p.62) (Spectrum C-7).

(1.2.3.2)<u>Ozonolysis of (169) and subsequent transformations</u>

Chemical manipulations of the functional groups of the side-chain of lactones are possible. For example, the acetylene (174) has been reduced[203] by hydrogenation over Lindlar catalyst to give the corresponding (Z)-alkene (175), in good yield, which was then cleaved to afford the aldehyde (176) by ozonolysis. This aldehyde could

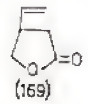
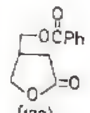
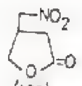
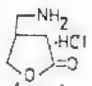
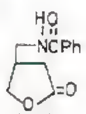


Scheme 32

be further subjected to homologation *via* a Wittig reaction[203] (Scheme 32). The aldehyde thus formed should be selectively reducible to the corresponding alcohol by employing mild reagents[204] (*e.g.*, sodium borohydride) even in the presence of the lactone moiety.

The alkene (169) (p.80) was ozonized successfully by ozone at -78^{o}. The resulting ozonide (171) was decomposed by dimethyl sulphide.[205] The mixture was then worked-up to give a gum, which was redissolved in methanol and treated with sodium borohydride. The alcohol (117) was obtained in quantitative yield. The spectral data of this compound are identical to those obtained previously. In characterizing the alcohol, the *O*-benzoate (173) was prepared by reacting the alcohol (117) with benzoyl chloride, in the presence of triethylamine. After purification, the ester (173) was isolated in 60% yield. The benzoate

Table 5 : High resolution PMR measurements of [illegible]-substituted γ-butyrolactones (at 200 MHz)

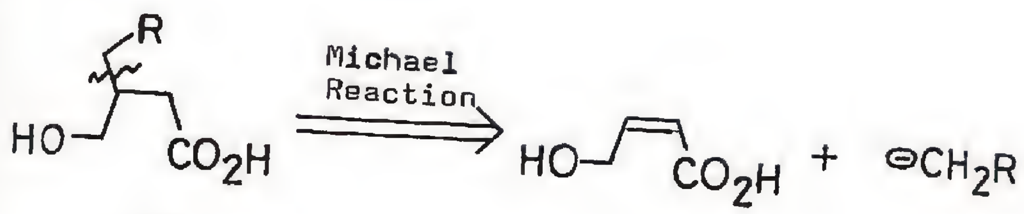
Compounds	Solvent	$H_{\alpha a}$	$H_{\alpha b}$	H_{β}	$H_{\gamma a}$	$H_{\gamma b}$	Hδ	(Hz) $\underline{J}(\alpha,\beta)$	(Hz) $\underline{J}(\beta,\gamma)$	(Hz) $\underline{J}(\beta,\delta)$	Other protons
 (169)	$CDCl_3$	2.41 (dd)	2.7 (dd)	3.22 (m)	4.03 (dd)	4.46 (dd)	5.8 (m)	8	8	8	δ 5.1-5.28(2H),(m) terminal olefinic protons
 (173)	$CDCl_3$	2.42 (dd)	2.51 (dd)	2.77 (m)	4.28 (dd)	4.56 (dd)	4.4 (dABq)	(a→b) 6 and 8	(a→b) 6 and 8	6	7.38-7.7 and 7.95-9.25(aromatic protons)
 (182)	$CDCl_3$	2.39 (dd)	2.86 (dd)	3.41 (m)	4.20 (dd)	4.6 (dd)	4.58 (dd)	(a→b) 7 and 9	(a→b) 6 and 7	7	
 (120a)	D_2O	2.54 (dd)	2.9 (dd)	3.1 (m)	4.22 (dd)	4.62 (dd)	3.21 (dd)	(a→b) 7 and 8	(a→b) 6 and 7.5	(a→b) 1.5 and 3	
 (183)	$CDCl_3$	2.36 (dd)	2.65 (dd)	2.93 (m)	3.51 (dd)	4.16 (dd)	4.40 (dABq)	(a→b) 6 and 8	(a→b) 5 and 7	6	δ 6.61(1H, broad s, N$\underline{H}$); δ 7.3-7.54 & 7.64-7.8 (m, aromatic protons)

was preferred to acetate because of the ease of detecting the product on TLC, and greater ease of separation of this less polar substance.

The peaks in the IR spectrum of this compound at 1765 and 1710 cm^{-1} can be assigned to the lactone and ester groups, respectively. As in the precursor, the α and γ methylene protons appear as doublet of doublets in the 200 MHz PMR spectrum. The newly produced exocyclic methylene protons are shown as an apparent doublet of triplets, while the methine proton becomes, a multiplet (Spectrum P-8, see Table 5) (p.84). The compound gives a clear-cut CMR spectrum allowing all the carbon resonances to be assigned (Spectrum C-8) (see p. 305).

(1.3) Synthesis of β-aminomethyl-γ-butyrolactone salts (120) by way of (b)-disconnection

(b)-Disconnection



(B) (H) (I)

In this disconnection, a one carbon fragment is attached to a preformed γ-lactone or acyclic analogue. The skeleton which may be utilized and still can be transformed into a γ-lactone is either a Δ^2-butenolide or the open-chain protected analogue.

A promising route is to use the Michael addition of carbon nucleophiles with unsaturated carboxylic acid derivatives. Here, the carbanion adds to the double bond regiospecifically at the β-carbon, thus giving a branch chain at the β-position of the lactone or ester.

(1.3.1) Michael addition to an unsaturated system

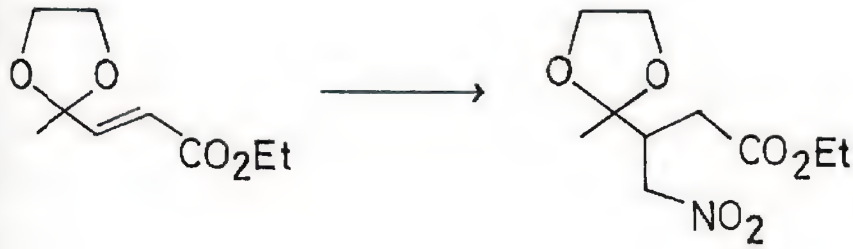
Michael addition of carbanions to α,β-butenolides has been extensively used for preparing β-substituted butyrolactones of interest in natural product chemistry, especially in the lignan field,[206] particularly *via* the carbanions of the lithio dithioacetals. Other carbanions used include those generated from vinyl or allylic organometallics,[207a] tri(methylthio)methyllithium,[207b] diethyl sodiomalonate and other salts of carbon acids,[207c-d] and anions derived from "activated" picolines,[208] used for producing cholinergic pilocarpine analogues.

Primary and secondary nitroalkanes[209] may react, in the presence of a basic catalyst, with α,β-unsaturated esters, aldehydes, ketones, cyanides, and related compounds, to give Michael adducts [*e.g.*, (179)]. A further stage of addition may occur when a primary nitro compound is

used. The basic catalyst is usually sodium ethoxide[210] or diethylamine[211] in an alcohol as solvent. Many other catalysts have also been used,[212] e.g., tertiary phosphines have been used by White[213] in the investigation of Michael addition of 2-nitropropane to activated olefins. Others include potassium fluoride[214] and tetrakis(triphenylphosphine)palladium[215] in the presence of a base(e.g., sodium methoxide). Furthermore, the Michael addition of doubly deprotonated, optically active β-hydroxy-carboxylates to nitroolefins have been achieved.[216] Of the various catalysts that have been employed, we were especially interested in the possible application of a phase-transfer catalysis system and of naked-anions (e.g., quaternary ammonium salts[217] and crown ethers[218]). For some general aspects of Michael addition, there are a number of extensive reviews available.[219]

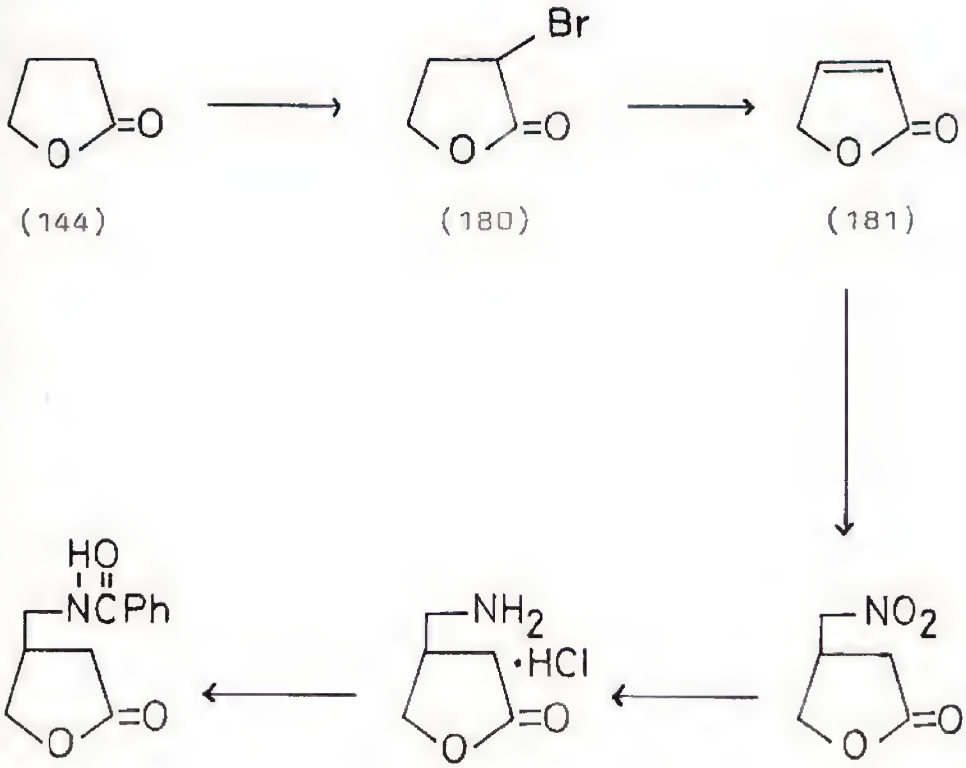
In our approach towards the β-aminomethyl-γ-butyrolactone (120), the appropriate synthon is nitromethane. The use of nitromethane as a substrate for organic synthesis is well-documented.[210-217] For example, Michael addition of nitromethane, in the presence of sodium ethoxide, to (178) (see p. 88) gives the ester (179) (Scheme 33)[210d]. In the present endeavour, tetra-n-butylammonium hydroxide is our choice of catalyst.

For the convenience of carrying out the discussion, the synthesis is divided into 2 groups identified by the intermediate on which the Michael condensation is



(178) (179)

Scheme 33



(144) (180) (181)

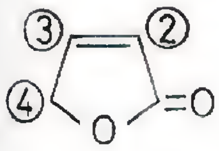
(183) (120a) (182)

Scheme 34

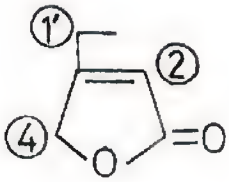
performed.

(1.3.2) $\Delta^{\alpha,\beta}$-Butenolide (181) as a Michael acceptor

The starting material, Δ^2-butenolide (181) was prepared from γ- butyrolactone by a halogenation-dehydrohalogenation process as reported by Price and Judge,[220] via α-bromo-γ-butyrolactone (180). The ^1H NMR spectral parameters of (181) are compared with data from other butenolides in Table 6A (p. 93) (see also Spectrum P-9). In the PMR spectra of butenolides, the following notations are employed, which can be found in Table 6A.

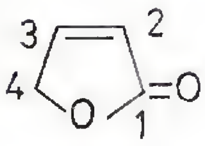


e.g., (181)

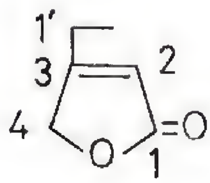


e.g., (202) (see p. 103)

The CMR spectrum of 2-butenolide (181) is much simpler. The following designations for the carbon atoms are adopted for butenolides:-



e.g., (181)



e.g., (202) (see p. 103)

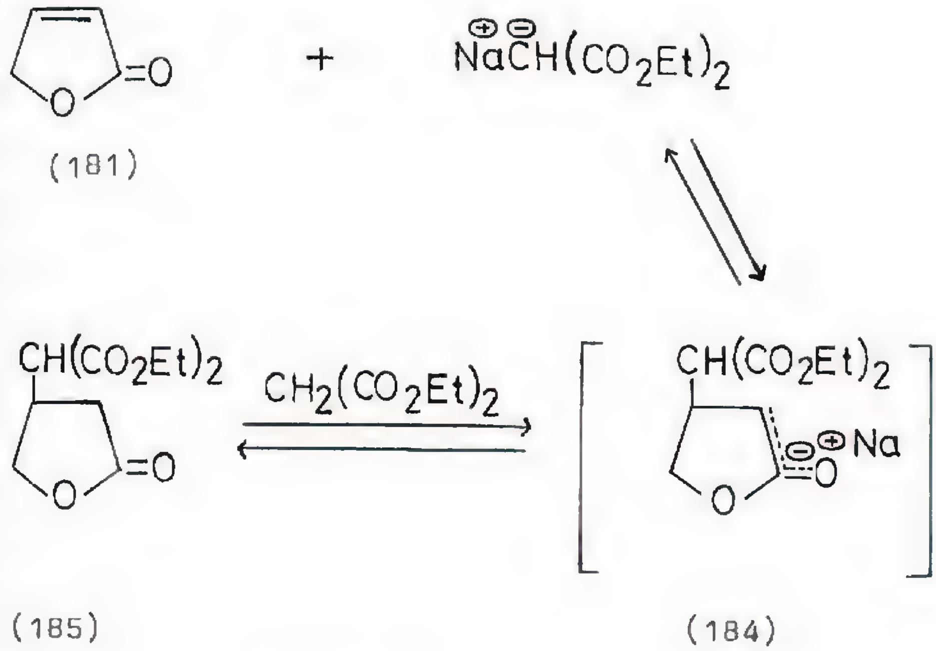
The assignments for these compounds are listed in Table

68 (see p. 94). The ^{13}C-NMR spectrum of (181) can be located in Spectrum C-9.

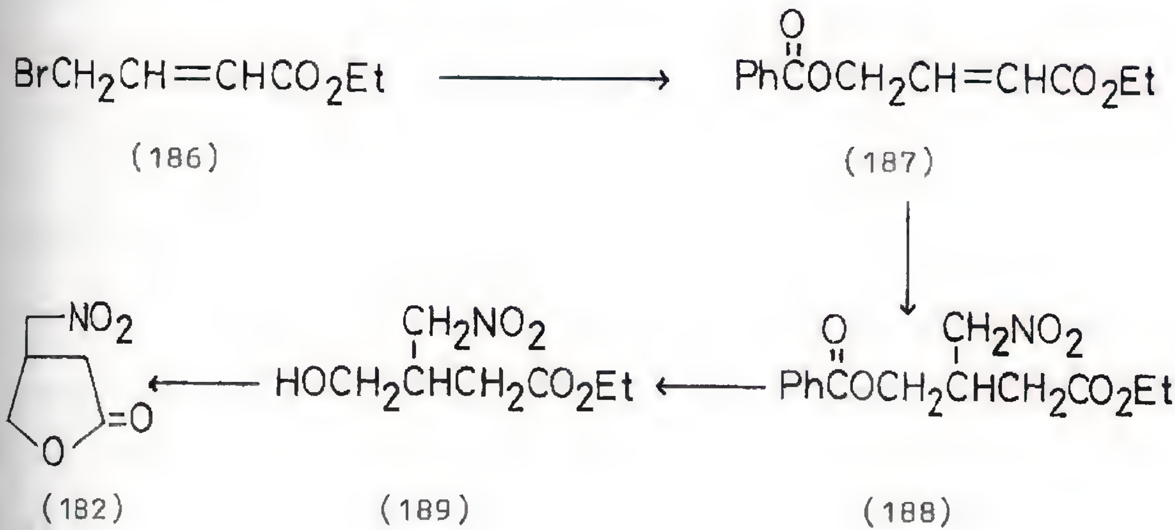
With the cyclic unsaturated ester (181) in hand, the hydronitromethylation was carried out using tetra-n-butylammonium hydroxide as catalyst under phase-transfer conditions[217] to give the nitromethyl lactone (182) in 30% yield (Scheme 34) (p. 88). A colour change (yellow to reddish-brown after adding base) was observed during the reaction, perhaps due to the colour of the generated carbanion. However, when 18-crown-6 with potassium carbonate was employed, the reaction time was much longer; the reaction was still not complete after 4 days, as judged by the PMR spectrum.

A mechanism of the reaction of 2-butenolide [e.g., (181)] with diethyl malonate has been put forward as shown in Scheme 35.[207c] The attack on the unsaturated lactone (181) by diethyl sodiomalonate results in a conjugated anionic species (184) which picks up a proton from diethyl malonate to afford the β-substituted lactone (185). A similar mechanism is presumably in operation for the nitromethylation reaction.

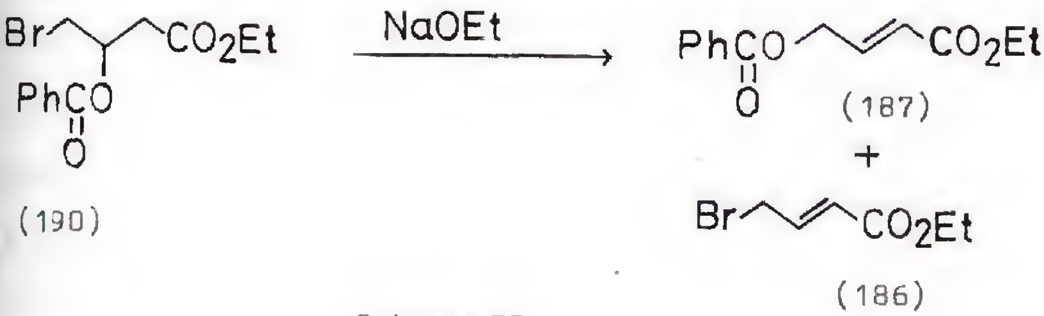
The IR spectrum of β-nitromethyl-γ-butyrolactone (182) (p. 88) shows a γ-lactone carbonyl peak at 1770 cm^{-1} and those of the nitro group at 1545 and 1350 cm^{-1}. In the PMR spectrum, 2 sets of doublet of doublets from the α protons are at δ2.4 and 2.86. The methine proton appears



Scheme 35



Scheme 36



Scheme 37

as a multiplet at δ 3.41. The γ methylene protons appear as two distorted doublets of doublets at δ4.2 and 4.6 respectively, while the exocyclic methylene protons resonate at δ4.58 as two almost overlapping doublets of doublets (Spectrum P-10, and Table 5) (see p. 84). The CMR determinations are listed in Table 3 (p.62). The most distinctive signal is that of the N-linked carbon atom at δ 76.3 (Spectrum C-10).

The reduction of the nitro compound (182) was achieved by hydrogenation on 10% palladium-on-charcoal, in the presence of dilute hydrochloric acid, in quantitative yield. The ammonium chloride (120a) was derivatized as the corresponding amide, which was checked by NMR and IR spectroscopies (see later for the full characterization of the N-benzoate, Section 1.5.1).

(1.3.3) Via open-chain α,β-unsaturated ester (187)

To examine the second proposition, the commercially available ethyl bromocrotonate (186) (see p. 91) serves as an ideal starting material. Allylic halides are reactive intermediates and their usage in organic chemistry has been reviewed.[221] The displacement of the bromide (186) with potassium benzoate generated from a mixture of benzoic acid and potassium carbonate gave the benzoate (187) in quantitative yield. The compound (187) has also been prepared, in 66% yield, during synthetic studies on ketene and its derivatives[222], as shown in Scheme 37, (190)$\rightarrow$(187) + (186).

Table 6A : PMR spectral parameters of 2-butenolides (at 200 MHz)

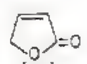
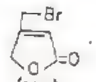
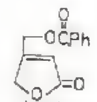
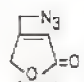
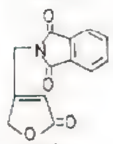
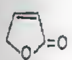
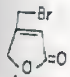
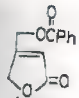
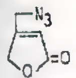
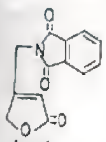
Compounds	Solvent	H-2	H-3	2H-4	2H-1'	$\underline{J}_{(2,3)}$ (Hz)	$\underline{J}_{(2,4)}$ (Hz)	$\underline{J}_{(3,4)}$ (Hz)	$\underline{J}_{(2,1')}$ (Hz)	Other protons
 (181)	$CDCl_3$	7.57 (dt)	6.15 (dt)	4.92 (dd)	-	6	1.5	2		
 (200)	$CDCl_3$	6.18 (dt)	-	4.97 (dt)	4.23 (dt)		1		1	
 (201)	$CDCl_3$	6.18 (dt)	-	4.95 (dt)	5.23 (dt)		2		1	δ 7.41-7.7 & 8.0-8.12 (5H,m,aromatic protons)
 (202)	$CDCl_3$	6.1 (dt)	-	4.83 (dt)	4.32 (dt)		1.7		1	
 (203)	acetone-d^6	6.19 (dt)	-	4.98 (dt)	4.50 (dt)		1.6		1	δ 7.85(4H,S, aromatic protons)

Table 6B : CMR assigments of 2-butenolides (at 15 MHz)

Compounds	Solvent	C-1	C-2	C-3	C-4	C-1'	Other Carbons
 (181)	$CDCl_3$	174.02	121.8	153.12	72.26	-	
 (200)	$CDCl_3$	173.1	118.88	164.19	72.13	22.85	
 (201)	$CDCl_3$	172.91	117.44	163.73	71.28	59.89	128.9,129. 94,134.04 and 166.01
 (202)	$CDCl_3$	172.97	117.77	163.6	71.54	48.17	
 (203)	acetone $-d^6$	174.61	119.01	165.81	72.46	23.89	123.82, 134.95 and 169.81

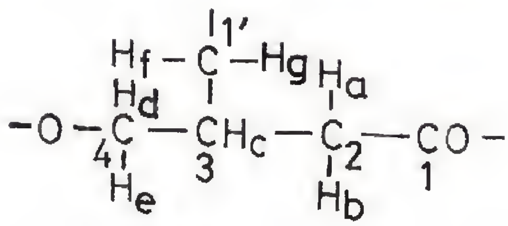
In the IR spectrum, the double bond stretching vibration is at 1655 cm^{-1}. The PMR spectrum of the α,β-unsaturated ester (187) shows a doublet of doublets, $\underline{J}$ = 2 and 4.5 Hz, for the allylic methylene protons, due to the couplings with the olefinic protons α and β, as illustrated in the diagram:

$$\underset{\gamma}{\overset{4}{-CH_2}}-\underset{\beta}{\overset{H^3}{C}}=\underset{\alpha}{\overset{H^2}{C}}-\overset{1}{CO}-$$

The γ-protons show as a doublet of doublets at δ 4.98 ($\underline{J}_{(4,2)}$ = 4.5, $\underline{J}_{(4,2)}$ = 2 Hz). The H-2 appears as a doublet of triplets at δ6.1, $\underline{J}_{(2,3)}$ = 16, $\underline{J}_{(2,4)}$ = 2 Hz, while the H-3 appears at δ 7.05, $\underline{J}_{(3,2)}$ = 4.5, $\underline{J}_{(3,4)}$ = 16 (Spectrum P-10). The two carbonyl carbon isotopes happen to overlap at δ166.01 in the ^{13}C-NMR spectrum of this compound. The allylic and the olefinic carbon atoms appear at δ 63.15, 122.58 and 141.59 respectively (Spectrum C-11).

As with Δ^2-butenolide (181), the α,β-unsaturated carbonyl compound (187) underwent Michael condensation with the nitronate ion in a regiospecific fashion to yield the β-nitromethylbutyrate (188) (Scheme 36) (p. 91). Due to sluggish manner in which the 18-crown-6 reaction was conducted previously, the employment of this catalyst was not attempted in this series.

The nitro group absorption signals in the IR spectrum of (188) are at 1540 and 1370 cm^{-1}. In the ^{1}H-NMR spectrum, the newly formed α methylene protons (H-2) appear as a doublet of doublets at δ 2.58:



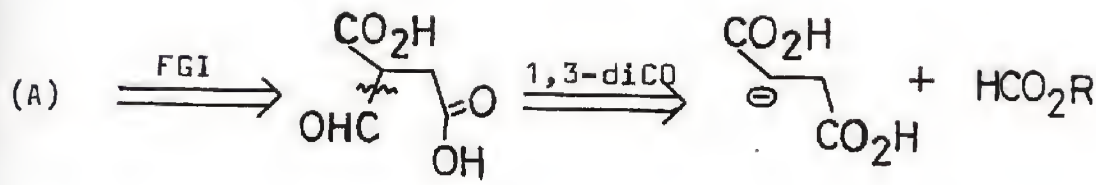
As in the diagram, (H-2) protons couple to (H-3) proton to give a doublet, with a coupling constant $\underline{J}_{(2,3)}$ = 7 Hz. These protons (H_a and H_b) are further split, long-rangely, by (H-1$'$) protons to two more doublets with coupling constants 2 Hz and ca.1.5 Hz respectively. The signals at δ 4.41 are assigned to the nitromethyl protons (H-1$'$). They also appear as a distorted doublet of doublets. Firstly, it is due to the coupling with (H-3) proton to provide a doublet, $\underline{J}_{(1',3)}$ = 7 Hz. Then these protons (H_f and H_g) are, in turn, coupled to the (H-2) protons *via* long-range coupling to give two doublets with finer splitting pattern, with coupling constants 1 Hz and 0.5 Hz. These long-range coupling patterns are only tentatively assigned since detail model-studies have not been conducted. The other methylene protons (H-4) appear as a doublet at δ 4.62, which is due to the coupling with (H-3) proton, with a coupling constant $\underline{J}_{(4,3)}$ = 7 Hz. Finally, the methine proton, (H-3 or H_c), couples with all the surrounding 6 protons to give a septet, with a coupling constant of 7 Hz (Spectrum P-12). In the CMR spectrum, the newly incorporated nitromethyl carbon atom resonates at δ76.17 (Spectrum C-12), which is comparable to that of the nitro lactone (182).

In order to complete the synthetic sequence, it is necessary to remove the benzoate ester group in compound (188) (p. 91) and to lactonize the resulting hydroxy ester (189). A similar sequence with the acetate (115) (see p.58) had been utilized to produce the hydroxy

lactone (117) (see Discussion, Section 1.2.1.4, Scheme 18). Thus the protected compound (188) was treated with sodium ethoxide in ethanol (1.1 equivalents), at room temperature. By TLC, however, only a small amount of the benzoate (188) was hydrolysed, surprisingly. Therefore, aqueous sodium hydroxide (again, 1.1 equivalents) was tried; there was only slightly more product formed. In the end, the mixture was refluxed for one hour and followed by an acid work-up to effect the ring closure. After column chromatography, the required product (182) was obtained in an overall yield of 4%, which had been identified by physical means, and most of the unreacted benzoate was also recovered, as indicated by TLC and NMR spectroscopy. However, there is no clear explanation for the experimental stability of the benzoate (188). Perhaps, it is due to the ionization of the nitromethylene group.

Since the nitro compound (182) could be more successfully prepared by the previous procedure, this became less important and was not pursued any further.

(1.4) <u>Attempted synthesis of the hydroxy lactone (117) by means of (c)-disconnection</u>

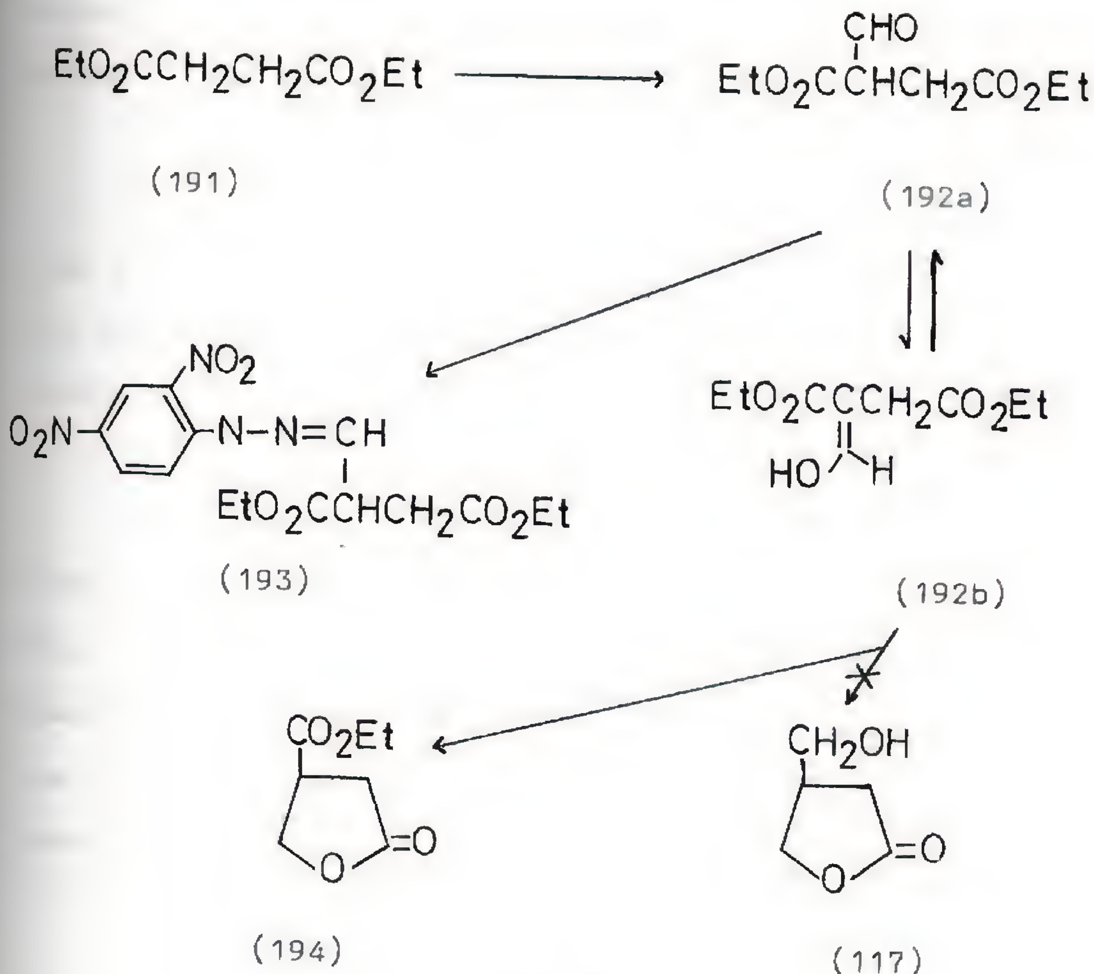


(J) (K) (L)

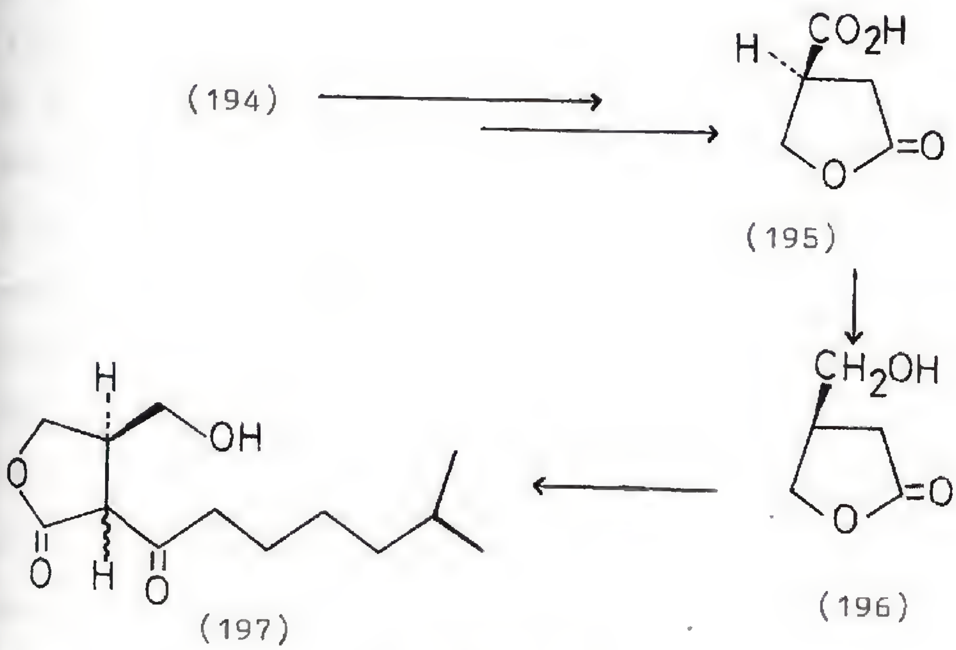
As indicated in the analysis of the disconnections (Discussion, Section 1.1), a new carbonyl group is introduced to the main molecule as a way of extending it by one carbon unit.

In some recent publications, the preparation of β-hydroxymethyl-γ-butyrolactone (117), which we had already made by a different route, has been reported and used in the synthesis of prostaglandin analogues.[223]

The stages involved in the preparation are presented in Scheme 38. To make the starting material, a Claisen condensation[224] is carried out on diethyl succinate (191) with ethyl formate. Diethyl 2-formylsuccinate (192) has been prepared and used in many occasions.[225] The most interesting of these examples is the conversion of compound (192) to succinic semialdehyde,[225b] a product of the transamination of GABA in its metabolism (see Introduction, Section 3.3). In our approach, sodium hydride was used[224b] as base. Thus the carbanion was obtained by careful addition of sodium hydride to a mixture of diethyl succinate and ethyl formate in diethyl ether. After the reaction, the product was purified by distillation in a yield of 61%. The formation of the formyl derivative (192) in the reaction could be checked by TLC. Because of the tautomerism between the aldehyde (192a) and the enol (192b) (Scheme 38), an elongated trace on the TLC plate



Scheme 38



Scheme 39

could be observed and the enolic product could also be stained with alcoholic $FeCl_3$ solution as a reddish brown streak.

The PMR and CMR spectra of the compound (192) show 2 sets of signals which arise from the presence of the two tautomeric forms, in a ratio of about 2 to 1 in favour of the oxo isomer (192a).

The formyl compound (192) was further characterized as its 2,4-dinitrophenyl hydrazone (193) by the usual procedure to afford orange colour crystals. This compound (193) has been made and characterized by Rosenthal and Elad.[226] The spectral data of this hydrazone are compatible with its structure (Spectra P-13 and C-13).

The reduction of the formyl ester (192) was carried out as described by Ishida et al.[223a] However, after work-up by distillation, the product showed different properties from those expected. It was much less polar than expected on TLC; there were 2 carbonyl peaks in the IR spectrum, one expected for a γ-lactone and the other characteristic of an ester. The presence of an ethyl group in the NMR spectrum confirms the compound as an ethyl ester. These spectral analyses of the product indicate a lactonic ester with a structure consistent with that of ethyl paraconate (194). Even after further treatment with sodium borohydride, only a trace of the desired hydroxy lactone (117) was observed on TLC. Anyway, the yield of this compound was

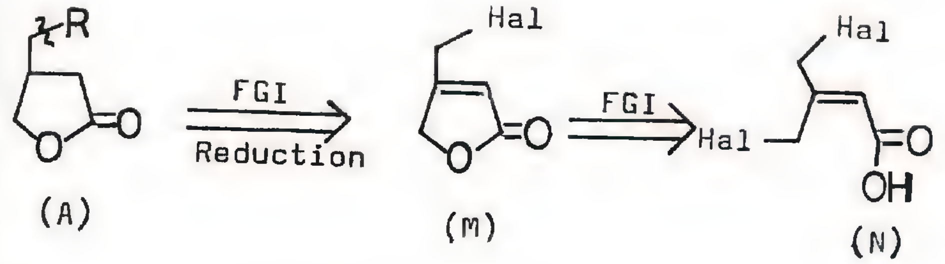
low and it was impossible to locate the required alcohol in any of the other fractions of distillate either. The CMR assignments of (194) are shown in Table 3 (p.62).

In theory, using excess reducing agent, which creates a sphere of nascent hydrogen around the most vulnerable aldehydic group, will induce attack as well at the ester group in its proximity, producing 2 hydroxymethyl groups. However, in reality, decomposition occurred together with the actual reduction.

Ethyl paraconate (194) has been prepared by the reduction of diethyl 2-formylsuccinate (192) with: (1) Al-Hg[225e] and (2) Raney Ni hydrogenation followed by elimination of ethanol at high temperature and pressure (70^{o}/20 mm.Hg).[225f]

The use of ethyl paraconate (194) to synthesize β-hydroxymethyl-γ-butyrolactone (117) and then to the inducer of streptomycin biosynthesis, A-factor, has very recently been published by Mori[227] as outlined in Scheme 39 (see p. 99). The compound (194) has been converted to paraconic acid (195) and resolved to this particular (S)-isomer,[225f,227] where the carboxy group is selectively reduced with borane- methyl sulphide (BMS)[144d] to the (S)-hydroxymethyl compound (196), one of the enantiomers of (117), and later to (197),[227] the (3R)-A-factor. The preparation of the (3S)-A-factor has also been, similarly, achieved.[228]

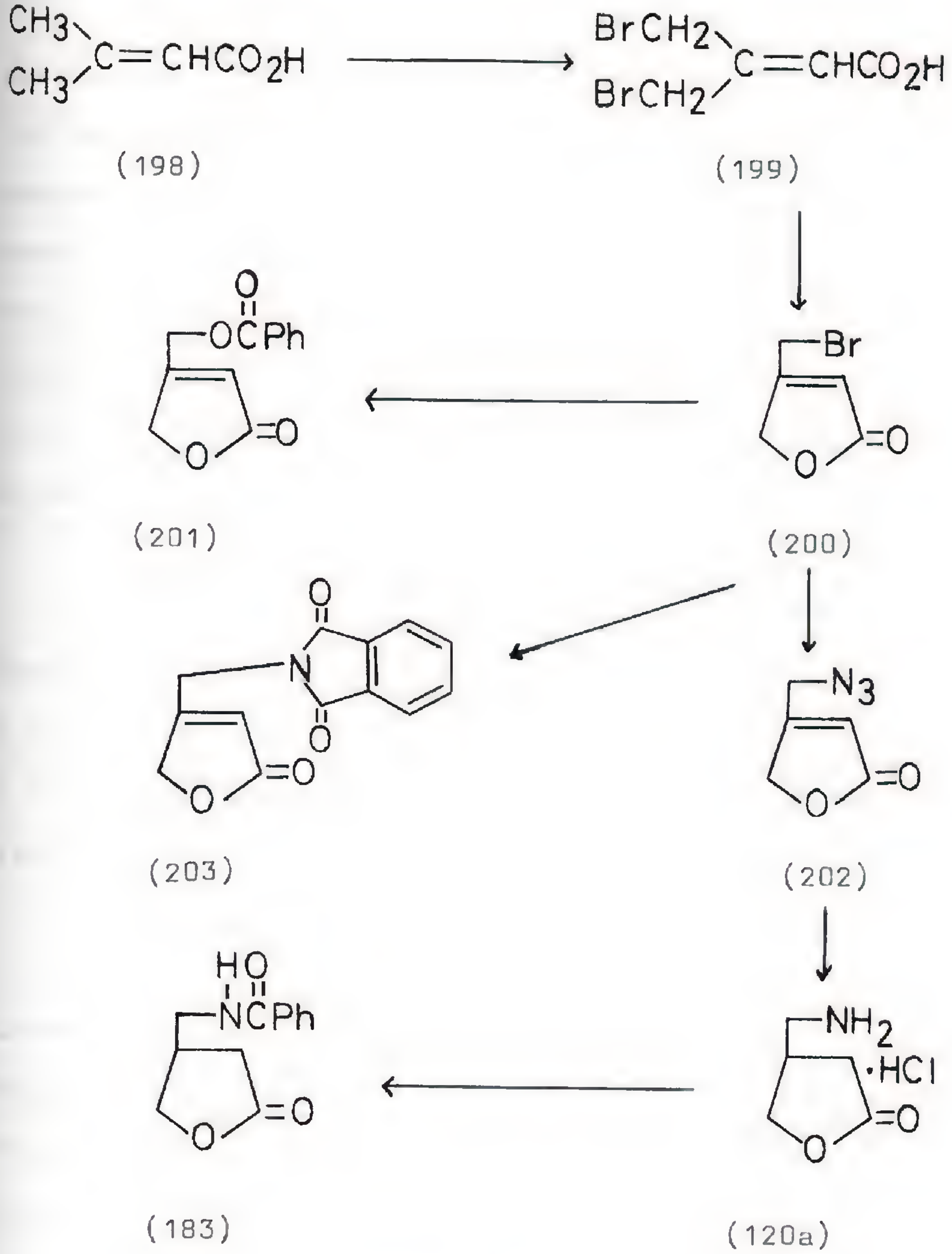
(1.5) Synthesis of β-aminomethyl-γ-butyrolactone salt (120a) by way of (d)-disconnection



No carbon chain construction is needed in this series. The required amine equivalent is introduced in the last but one step. This is very similar to the later stage of the approach via a Wittig-Horner reaction (Discussion, Section 1.2.1). The amino lactone (120) (see p. 71) is also proposed to be formed by means of catalytic hydrogenation.

As in the allylic bromide [e.g., (186)] (p. 91), nucleophilic displacement will produce an heteroatam linked allyl compound (also see Discussion, Section 1.3.3). Thus an allyl halide which is attached to a lactone ring [e.g., (200)] will be the choice for this disconnection. Indeed this should give the required azidomethyl γ-lactone [e.g., (202)] by azidolysis easily.

The bromomethyl lactone (200), which is ideally suited for the transformation was prepared, and its conversion to various aminomethyl derivatives is illustrated in Scheme 40.



Scheme 40

(1.5.1) Preparation

3,3-Bis(bromomethyl) acrylic acid (199) was obtained by the bromination of 3,3-dimethylacrylic acid (198) at the allylic positions with N-bromosuccinimide induced by a radical initiator, benzoyl peroxide, in quantitative yield.[229,230] Without purification, the bromo acid (199) was cyclized to the corresponding β-bromomethyl-2-butenolide (200) in 83% yield using exactly one equivalent of base, sodium hydroxide, according to the method of Boeckman.[230]

To study the chemical properties of the allylic bromide (200), the novel benzoate (201) was synthesized by the reaction of the bromide (200) with benzoic acid in the presence of anhydrous potassium carbonate. The yield of this product was 78%.

The compound (202) was formed by the azide displacement of the bromide with sodium azide, using aqueous acetone as solvent. After purification, the azide (202) was obtained as an oil in 75% yield. This was hydrogenated with 10% palladium-on-charcoal with a mixture of ethanol and 1 N aqueous hydrochloric acid to give the amine salt (120a) by the incorporation of one molecule of hydrogen to the 2-butenolide and one to the azide with the concurrent elimination of one molecule of nitrogen. It is interesting to know that $\Delta^{\alpha,\beta}$-butenolides can be reduced by catalytic hydrogenation,[231,232] while the $\Delta^{\beta,\gamma}$-butenolides are converted, sometimes, to mixtures of the buta-

nolides and the corresponding desoxy acids or just to the ring-cleavage compounds. The ammonium chloride (120a) was successfully N-benzoylated with benzoyl chloride and with triethylamine as base. It was isolated, in 61% yield, as a light yellow solid.

The phthalimido compound (203) was prepared by reacting the bromide (200) with potassium phthalimide in N,N-dimethylformamide for 50 minutes. However, there were signs of decomposition, or perhaps some Michael addition via the nitrogen anion had occurred.[233] After purification, a high meeting solid was obtained in 45% yield.

Some GABA analogues are in the form of amides (either straight chain or cyclic) (see Introduction, Section 4) and they do possess activities as GABA-mimetics. Since this compound (203) is an amide and also an analogue of GABA, it was intended to test it as it is. Since the compound is also a lactone, conversion of this amide to the corresponding amine was not attempted.

(1.5.2) Spectral characterization

In the IR spectra of all the butenolides two peaks at 1760 and 1730 cm^{-1}, which are characteristic of $\Delta^{\alpha,\beta}$-butenolides, are observed. The benzoate (201) also shows a third carbonyl signal at 1715 cm^{-1} for the ester group. The compound (202) has an azide band at

2100 cm^{-1}, while the phthalimide (203) shows a secondary amide peak at 1720 cm^{-1}. After hydrogenation of the azide, the signal at 2100cm^{-1}, disappeared, being replaced by a broad ammonium chloride band at ca. 3200-2500 cm^{-1}, with a peak for the γ-lactone at 1770 cm^{-1}. The N-benzoate (183) shows bands at 3450 cm^{-1} (amide H), 1770 cm^{-1} (γ-lactone) and 1660, 1530 cm^{-1} (amide I and II).

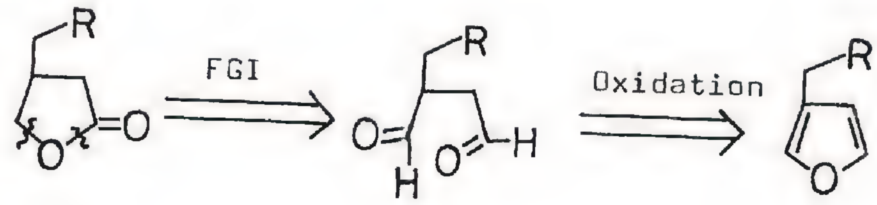
The notations used for the ^{1}H- and ^{13}C-NMR spectral interpretation are explained (see p.89). In the PMR spectra of compounds (201) and (202), homoallylic coupling is observed between the olefinic proton and both methylene protons of the ring and of the exocyclic branch [Spectra P-14 for the benzoate (201) and P-15 for the azide (202) and phthalamide (203)] (see Table 6A for spectral details) (p. 93).

The PMR spectra of both the salt (120a) and the benzamide (183) (Spectra P-16 and P-17, respectively) show the same pattern as in the previous high resolution NMR measurements (see Table 5) (see p. 84). In the amine salt, the N-CH_2 signal is at δ3.2 and the corresponding signal for the amide (183) is at δ3.5.

The CMR spectra of these compounds are much simpler.[234] The carbon isotopes (C-2 and C-3) in the butenolides usually resonate at ca.δ118 and 164 respectively and these, after hydrogenation [e.g., the azide (202)→the salt (120a)], shift to δ34 and 32. The

resonance of the C-1' carbon signal depends on the substituent [e.g., in the bromide (200) at δ 22.9 while in the benzoate (201) at δ 59.9]. The data for the butenolides being listed in Table 6B (p. 94) [benzoate (201) (Spectrum C-14) and azide (202) (Spectrum C-15) and phthalimide (203)] and for the butanolides in Table 3 (see p.62) [salt (120a) (Spectrum C-16) and amide (183) (Spectrum C-17)].

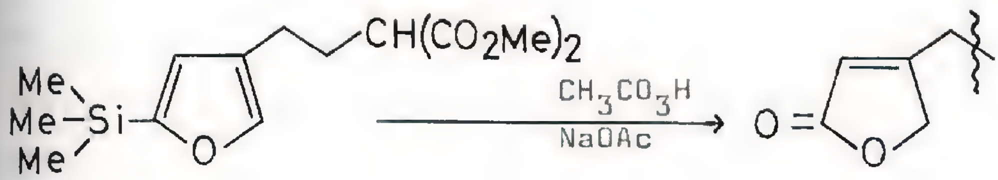
(1.6) Photooxygenation of furans : (e)-disconnection



(A) (O) (P)

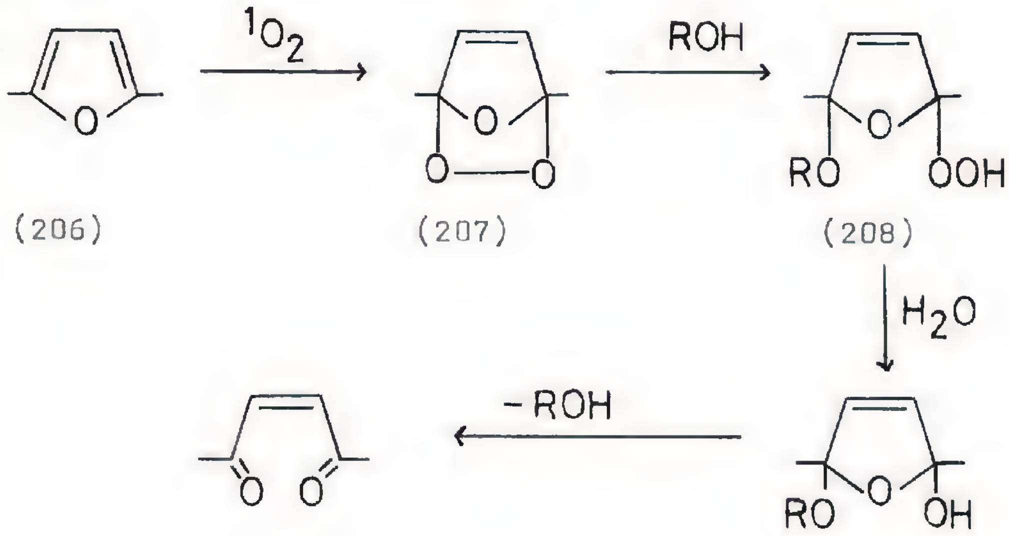
The preparation of butenolides and γ-butyrolactones from furans has been reported recently. These methods include singlet oxygenation,[235] electrolysis[236] and peracid oxidation.[237] For example, silylated furan (204) can be readily oxidized by peracetic acid[237a] to the 3-substituted butenolide (205) in 78% yield (Scheme 41).

The oxidation of furans with singlet oxygen has had widespread application in organic synthesis. This oxidation, which takes place through an initial 1,4 endoperoxide, leads to many different types of products depending on the reaction conditions.[238] The formation



(204) (205)

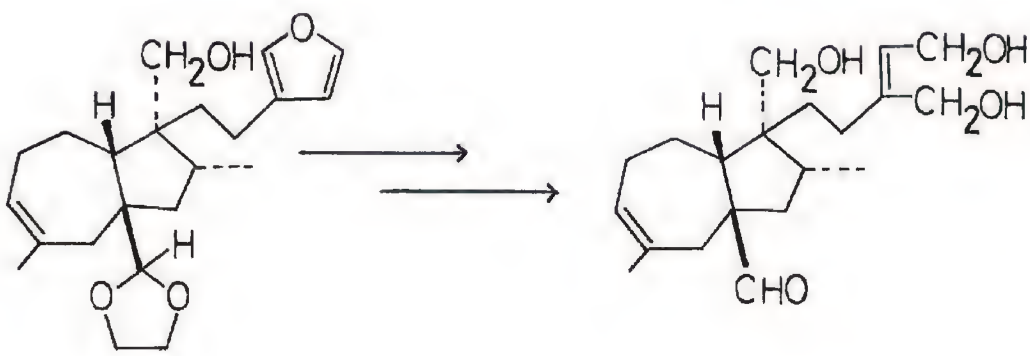
Scheme 41



(206) (207) (208)

(210) (209)

Scheme 42



(211) (212)

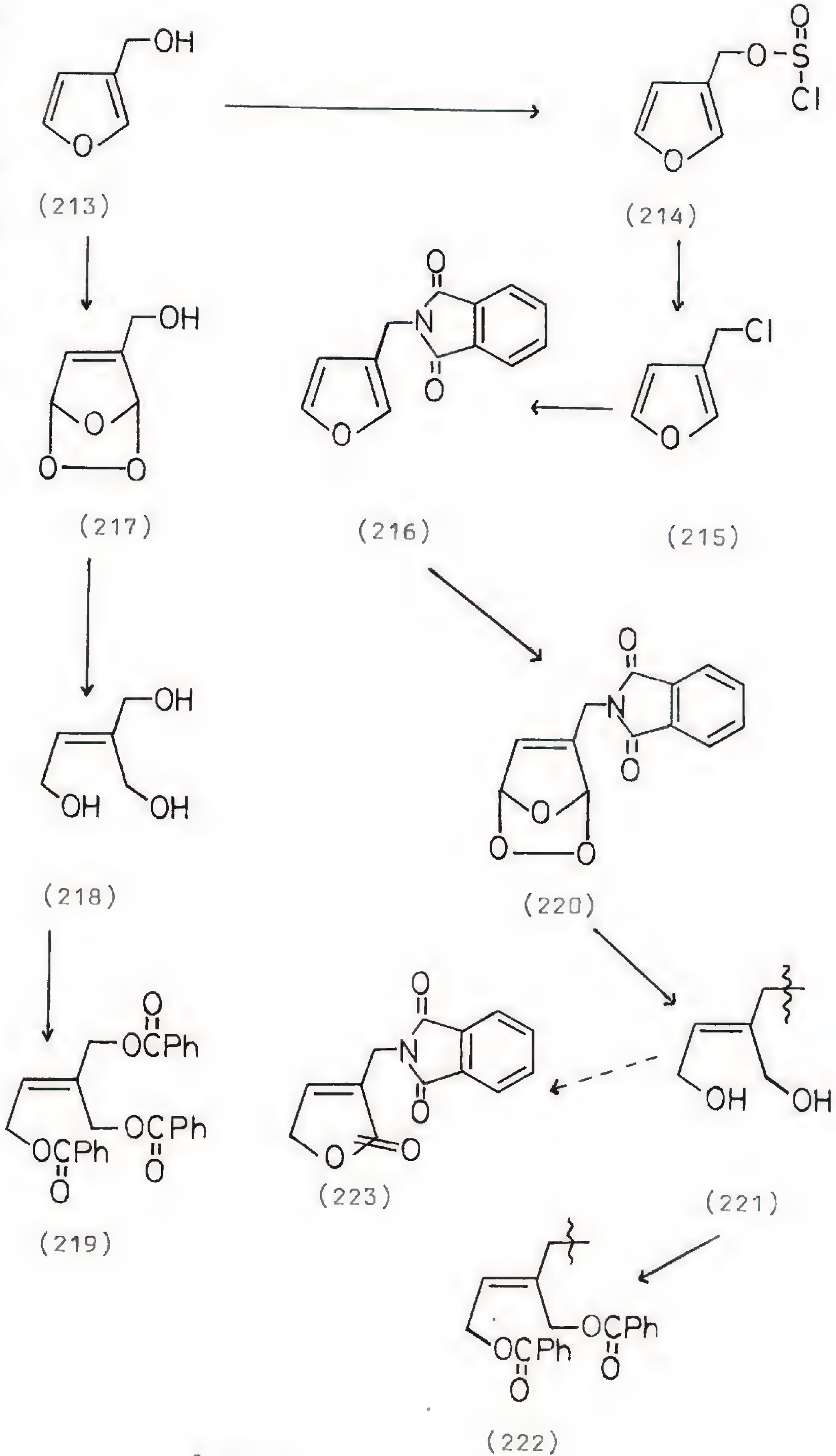
Scheme 43

of enediones by the reaction of furans with singlet oxygen in alcoholic solvents appears to occur by the solvolysis of initially formed endoperoxides to yield alkoxy hydroperoxides which may be hydrolyzed to the corresponding enediones as shown in Scheme 42. This we can visualize without the need of too much imagination is due to an (e)-disconnection, when the keto groups [e.g., (210)] is replaced by aldehydic functions. As in the total synthesis of portulal,[235a] the 3-substituted furan (211) has been photoöxygenated and then reduced to the precursor of the natural product and finally to portulal(212) (Scheme 43). A diol such as (212) could be converted to a butenolide by oxidation (see Introduction, Section 5.1.3) and further elaborated to the required aminomethyl compound.

We planned to use a protected aminomethylfuran [e.g., (216)] as our starting material for this particular transformation, which will be projected to give an isomeric mixture of the phthamidomethylbutenolides (216)→(221)→(223) (Scheme 44).

(1.6.1) Preparation of the phthalimide (216)

The chloride (215) was prepared by a literature method.[239] However, in the first run, about 20% of the product was contaminated by a second compound, showing a methylene proton signal at δ 4.9 (ABq, J = 12 and 18 Hz) in the PMR spectrum. It was assumed to be the ester (214). This was retreated with thionyl chloride to give one product in 62% yield. Recently, an improved procedure



Scheme 44

has been published[240] using mesyl chloride, lithium chloride and S-collidine as base in 80-85% yield.

The chloride (215) was converted to the phthalimide (216) in 41% yield by the usual procedure. A brown solid, melting at 74-76^{0}, was obtained which turned darker in colour on storage at room temperature for two to three days. Spectral analyses by PMR and CMR are shown in Spectrum P-18 and Spectrum C-18.

(1.6.2) Singlet oxygen oxidation

To test out the reaction, the readily available alcohol (213) was used. Sensitized photooxygenation[241] (with methylene blue) of the furan, at -78^{0}, was complete within one hour. Without isolation, the resulting endoperoxide (217), which would behave as an ozonide, was reduced with either vitride [$NaAlH_2(OCH_2CH_2OCH_3)_2$] or sodium borohydride. The triol (218) was indicated to be present in the product by PMR spectroscopy. Thus attempts were made to characterize the alcohol as the benzoate (219). However, after purification, only a small yield of the impure compound (219) was obtained. The phthalimide (216) was similarly oxidized, reduced, and benzoylated. As before, only some of the required product was formed, as judged by the NMR spectrum.

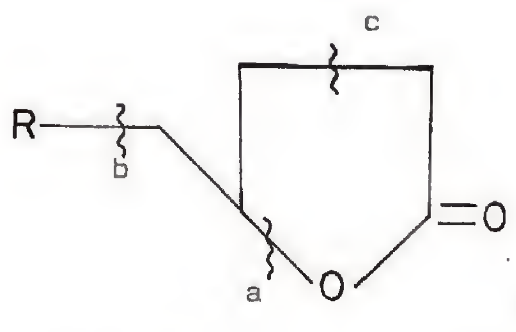
Since this reaction did not seem to offer a promising route to the required butenolide, this approach was abandoned.

(2) Preparation of γ-aminomethyl-γ-butyrolactones [e.g., (232)]

On examination of the structure of γ-aminomethyl-γ-butyrolactone [e.g., (232), see p.115], we should realize that it can overlap with the amino-lactone part of bicuculline (3) (see p.16). As before [in the β-aminomethyl-γ-butyrolactone (120) (see p.54) case, Discussion, Section 1], examination of the structure of (232) using Dreiding models indicates that it closely resembles an extended GABA conformation (5). In fact, this compound is more an analogue of bicuculline than that of γ-aminobutyric acid (GABA).

(2.1) Strategies of synthesis

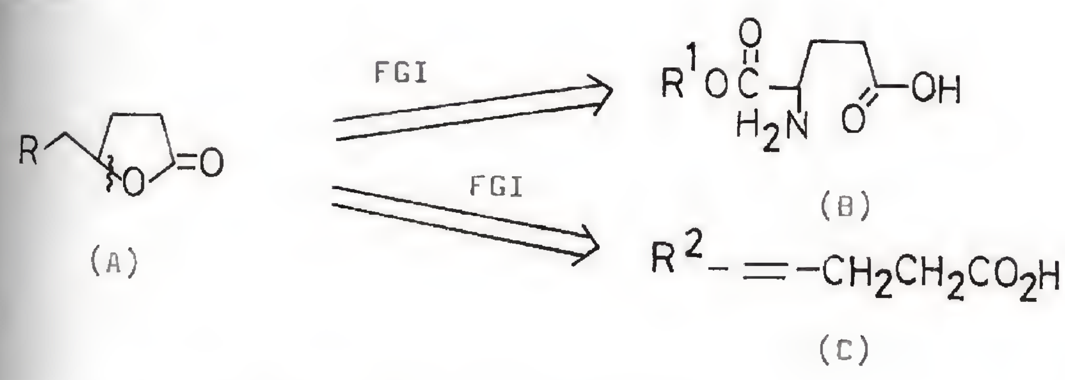
The same disconnection method[148] was used to study the construction of the target molecule [e.g., (232)]. However, considerably less work has been done by us on this derivative. Only those disconnections will be mentioned which we have attempted to utilize and are shown as follows.



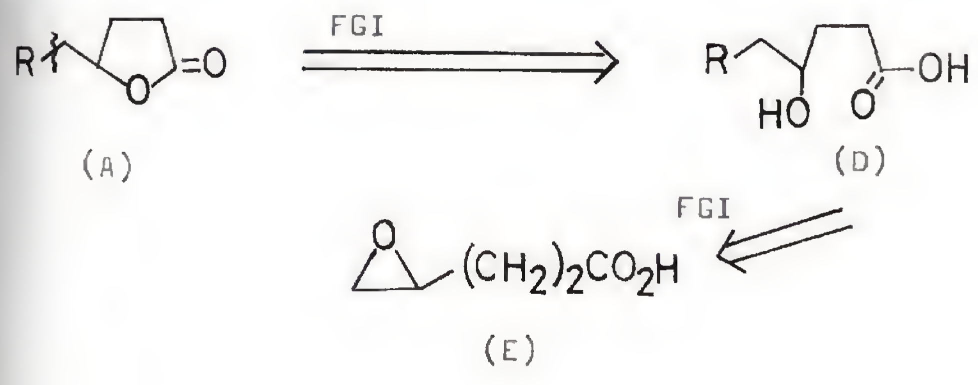
(A)

The retrosynthetic analysis of the molecule (A) suggests the following possibilities [using the same terminology as before (Discussion, Section 1)].

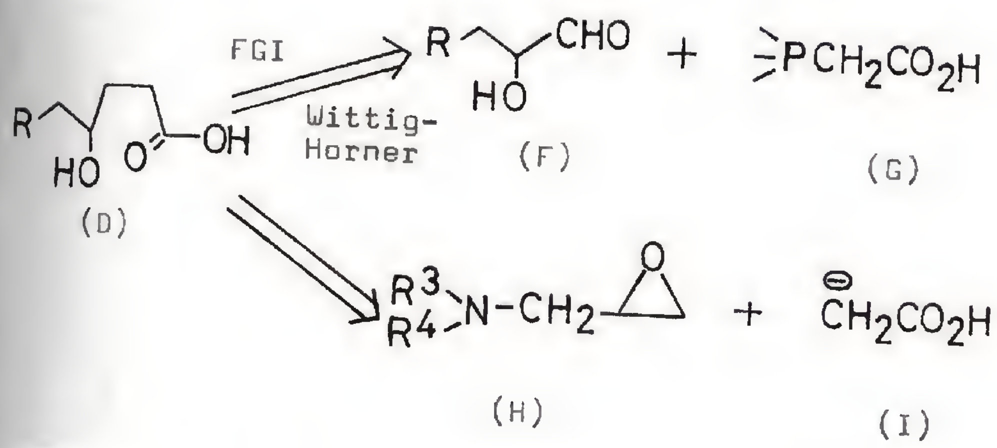
(a)-Disconnection



(b)-Disconnection



(c)-Disconnection



(2.2) Synthesis by means of (a)-disconnection

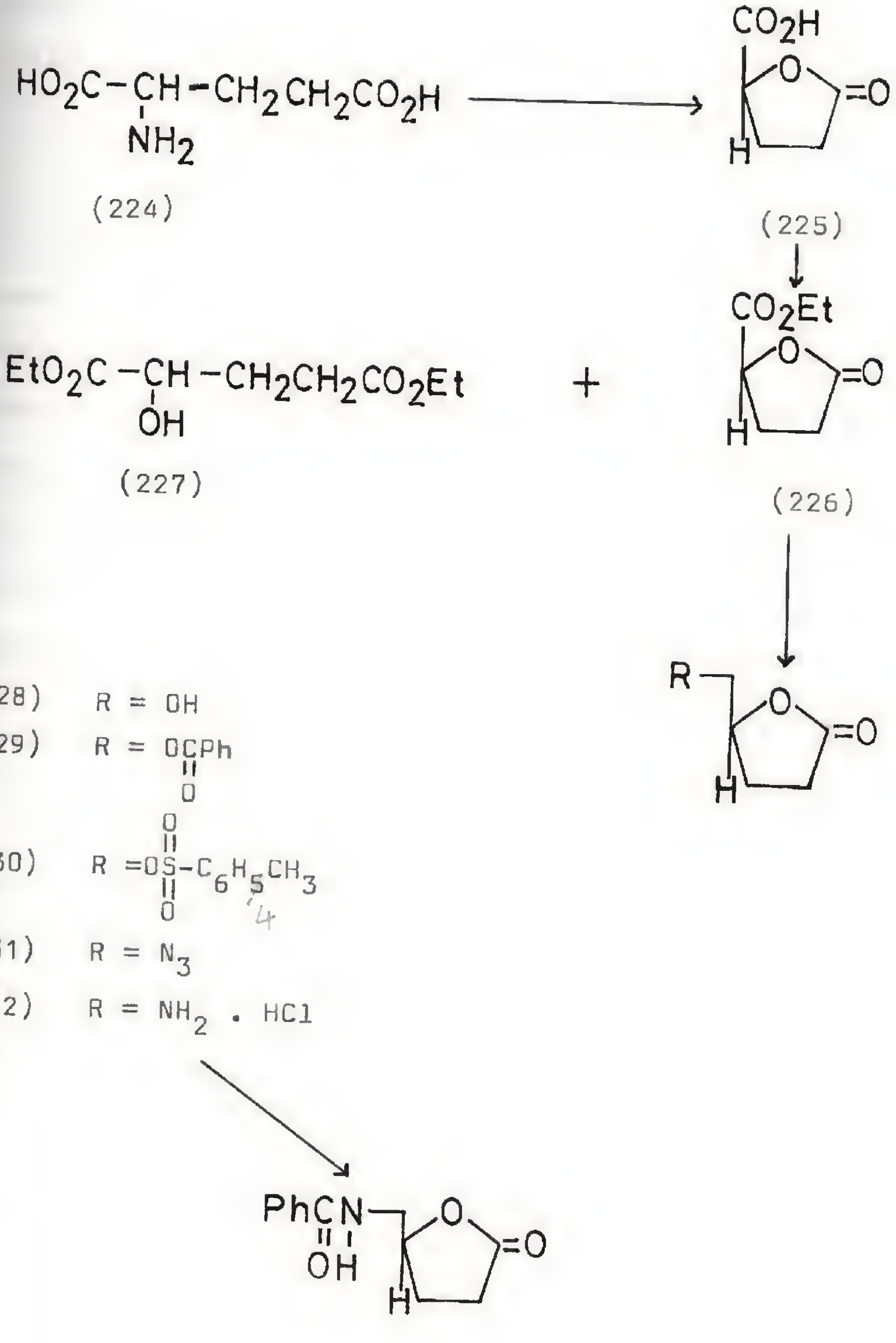
As indicated in the strategy section, this disconnection can be fulfilled by two routes: via the deamination of glutamic acid and by an iodolactonization of an ω-unsaturated acid

(2.2.1) Preparation of (S)-γ-aminomethyl-γ-butyrolactone salt [e.g., (232)] via the deamination of L-glutamic acid

The stages involved in the synthesis are present in Scheme 45.

(2.2.1.1) Synthesis of (S)-4-hydroxymethyl-γ-butyrolactone (228)

The asymmetric γ-hydroxymethyl-γ-lactone (228) can be constructed from either the amino-acid, L-glutamic



(224)

(225)

(226)

(227)

(228) R = OH

(229) R = OC(=O)Ph

(230) R = $OSO_2-C_6H_4CH_3$

(231) R = N_3

(232) R = NH_2 . HCl

(233)

<u>Scheme 45</u>

acid (224), by the present disconnection or from a carbohydrate synthon as in (c)-disconnection (Discussion, Section 2.4) (see p. 138).

The utility of this enantiomeric synthon (228) as a building block for asymmetric synthesis is well-known.[242] The following examples are taken from those which actually use the optically active compound derived from L-glutamic acid [(S)-glutamic acid]. It has been used in the syntheses of a component of Trogoderma insect pheromone,[242a] of γ-methyl-α-methylene-γ-butyrolactone,[242b] of its less accessible (R)-(-)-enantiomer[242c] and also of D-ribose.[242d]

Thus L-glutamic acid was converted stereospecifically, without inversion, to the (S)-4-carboxy-γ-butyrolactone (225) <u>via</u> deamination using nitrous acid as described,[242d,243] in quantative yield. The mechanism of this reaction is believed to involve double inversion, thus giving overall retention of configuration.[244,245]

On TLC analysis, compound (225) only gave a streaky trace. Although a greenish coloration gradually developed on storage, and a minute amount of reddish-brown fume was given off when the container was exposed to air (perhaps due to some nitrous acid being retained with the syrupy acid), it proved sufficiently pure to use for the next stage. This was confirmed by the high yields of the esters [(226) and (227)] (see later).

Spectral analysis of this compound indicated that it contained some acyclic α-hydroxyglutaric acid. In the IR spectrum of (225) the lactone carbonyl signal at 1780 cm^{-1} was considerably weaker than a normal lactone C=O peak. In the present case it was only as strong as the carboxylic signal at 1715 cm^{-1}. A very complex spectrum was observed by PMR spectroscopy. Furthermore, the ^{13}C-NMR spectrum (see Table 7 on p.121) suggested that about 20% of a second compound was present, as indicated by the relative intensity of the peaks.

Esterification of the acid using ethanol with p-toluenesulphonic acid as catalyst (without removal of all the solvent) gave the hydroxy diester (227) (see p.115) in quantitative yield. TLC and NMR analysis suggested that there was only about 10% of the lactonic ester (226) present. To maximize the yield of the ester, the work up procedure was modified. The solvent was evaporated as far as possible, and the residual syrup subjected to the usual aqueous work-up. The residue was purified by distillation to give a light yellow oil, considered from spectroscopic and TLC evidence to be mainly the monoester (226). The C-13 NMR measurements of this compound (226) are listed in Table 7 (p.121). The original report[242d] on the preparation of the lactone (226) does not mention the formation of the diester (227) simultaneously, although this by-product is mentioned in a paper from another laboratory.[242a] However, this must be a persistent phenomenon, since the treatment of the

hydroxy diester (227) with neat trifluoroacetic acid also furnished the lactonic ester (226) in ca. 90% purity, with the rest being in the open-chain form, judging by G.C. analysis.

Selective reduction of the ester (226) had been effected by the use of sodium borohydride in ethanol. The desired hydroxymethyl-γ-lactone (228) was obtained in 51% yield after careful column chromatography.

The hydroxy lactone (228) has also been prepared from the lactonic acid (225) by reduction with borane-methyl sulphide (BMS)[242b,e] (for the use of BMS in the β-aminomethyl series see Discussion, Section 1.4).

The IR spectrum of the compound (228) shows a broad OH band and a strong γ-lactone carbonyl signal at 3400 and 1765 cm^{-1} respectively. There are 2 bands of signals between δ2 and 2.8 and between δ3.4 and 4 for the α, β and exocyclic methylene protons in the PMR spectrum. The multiplet at δ4.55 belonges to that of the methine proton (Spectrum P-19). The CMR spectrum of the alcohol gives a simple pattern of carbon atom resonances (Table 7, Spectrum C-19) (see p. 121).

The alcohol (228) was characterized as the corresponding O-benzoate (229), using benzoyl chloride with Et_3N. Compound (229) was obtained after purification, as a light yellow oil, in 50% yield. This compound shows 2

carbonyl signals at 1780 and 1720 cm^{-1} for the γ-lactone and the benzoate, respectively. The exocyclic methylene protons appear as an ill-defined doublet of doublets in the 100 MHz PMR spectrum (Spectrum P-20). The CMR spectrum of the benzoate (229) shows a simplified picture compared to ^{1}H-NMR (Table 7, Spectrum C-20).

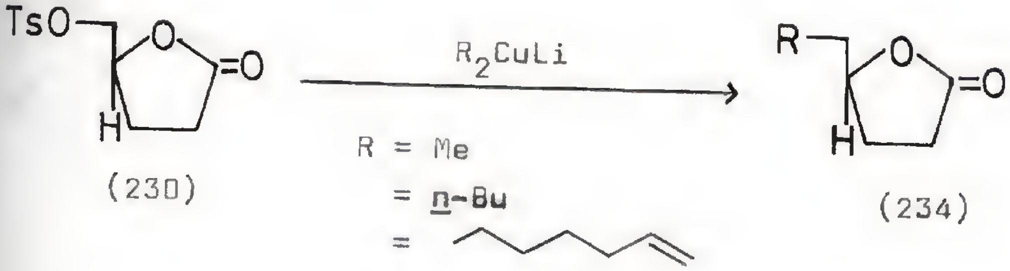
(2.2.1.2) <u>Preparation of (S)-4-tosylmethyl-γ-butyrolactone</u>

The tosylate (230) (see p.115) has been made and used in chemical syntheses.[242a-c] In the study by Silverstein,[242a] (230) reacts preferentially with lithium di-alkylcuprates to give the chain extended γ-lactones (234) (Scheme 46), without affecting the ring and its stereochemistry. The tosylate (230) has been converted to the two enantiomeric γ-valerolactones (236) and (238) as outlined in Schemes 47[242b] and 48[242c] (see p.120). To prepare the (S)-enantiomer (238), the lactone was ring-opened to give the epoxide, which was then lactonized with trifluoroacetic acid to provide the necessary inversion of configuration.[242c]

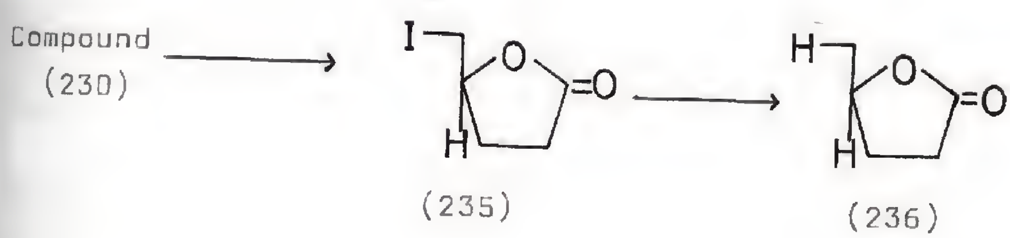
Preparation of the tosylate (230) was conveniently performed as for the <u>O</u>-benzoate, rather using the conventional pyridine method.[242a-c] The required crystalline product was obtained in 50% yield.

The PMR spectrum of the compound (230) shows the lactonic methine proton at δ4.55 and the expected ABq

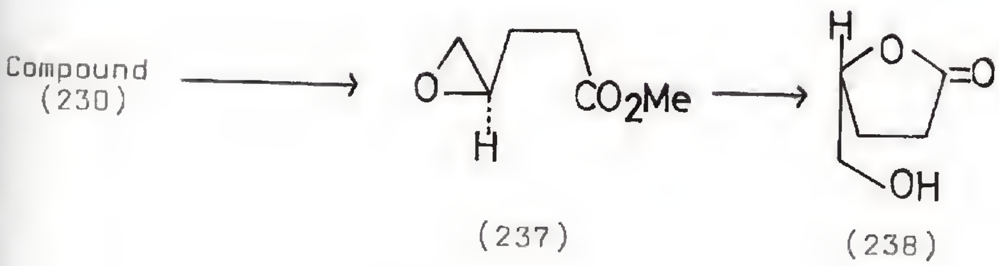
pattern of the aromatic protons (Spectrum P-21) and the CMR analysis is listed in Table 7 (p.121) (Spectrum C-21).



Scheme 46

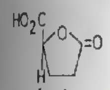
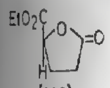
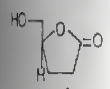
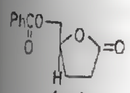
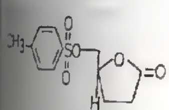
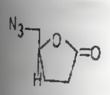
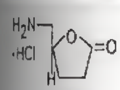
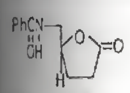
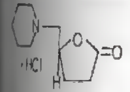


Scheme 47



Scheme 48

Table 7 : CMR spectral parameters of some (S)-γ- substituted γ-lactones

Compounds	Solvent	C-1	C-2	C-3	C-4	C-5	Other carbons
 (225)	D_2O + 1,4-dioxane	178.5	30.0	29.2	69.9	178.3	
 (226)	$CDCl_3$	176.4	26.8	25.9	75.9	170.3	14.1 and 62.1
 (228)	$CDCl_3$	178.3	28.7	23.1	81.1	64.1	
 (229)	$CDCl_3$	176.8	28.2	24.0	77.5	65.8	128.7,129.9,133.6 and 166.4
 (230)	$CDCl_3$	176.4	27.9	23.5	76.6	70.1	21.7,128.2,130.2, 132.4 and 145.7
 (231)	$CDCl_3$	176.6	28.2	24.6	78.1	54.2	
 (232)	D_2O + DSS	185.7	30.8	27.1	80.6	45.5	
 (233)	$CDCl_3$	177.21	28.58	24.86	79.75	43.42	127.27,128.83,132.09 and 133.98
 (246b)	D_2O + 1,4-dioxane(reference to absolute zero)	219.19	66.14	60.54	113.54	91.33	59.83,63.34 and 82.94

(2.2.1.3) Synthesis of the asymmetric azide (231) and subsequent reduction to the ammonium chloride (232)

Even though the preparation of this azide (231) by way of the chiral synthon (228) (see p.115) from L-glutamic acid is novel, (S)-(+)-4-azidomethyl-γ-butyrolactone (231) is a known compound, which has been made by Inch in the synthesis of S(-)piperidin-3-ol (243)[246] from mannitol as outlined in Scheme 49 (see p.125).

The displacement reaction of the tosylate (230) with sodium azide using aqueous acetone as solvent resulted in decomposition, although these conditions had been successfully employed in the β-series (see Section 1.2.1.6). However, azidolysis in N,N-dimethylformamide did give the required azido compound (231) in 87% yield after chromatography, which was pure by gas chromatographic analysis.

In the IR spectrum of this compound (231), the azide signal appears at 2100 cm^{-1}. Its PMR spectrum is consistent with the assigned structure. In the ^{13}C-NMR spectrum, the N_3CH_2 carbon isotope resonates at δ 54.2 [compared with that of the tosylate (230) at δ70.1] (Table 7) (p.121).

The reduction of an azido lactone [e.g., (231)] will produce an amino lactone (244), which, under non-

acidic conditions, can rearrange to a lactam (245) Scheme 50, (see p.125). This is observed in the synthetic studies of squamolone.[247]

Thus catalytic hydrogenation of the azide (231) (see p.115) in an acidic medium gave the ammonium chloride (232) in quantitative yield. The azide signal had disappeared from the IR spectrum of this compound (232) and instead a broad NH_3^+ band was observed. The NMR spectra show very complex patterns. Even in the CMR spectrum, the usually simple pattern became much more complicated as a shadowy second set of singnals appeared. We assumed that these weaker resonances belonged to the open-chain form (about 30%), with the lactone signals being appropriately duplicated at δ31.7, 32.4, 47.1, 60.2 and 189.1. The carbon atom assignments of the major component are presented in Table 7.

The hydrochloride (232) was derivatized as the corresponding benzamide (233), by the usual procedure. The amide (232) was formed in 89% yield as a creamy gum after chromatography. Formation of the N-benzoyl lactone in high yield indicates that under the reaction conditions, any acyclic acid form present in equilibrium in the initial material is transformed to lactone.

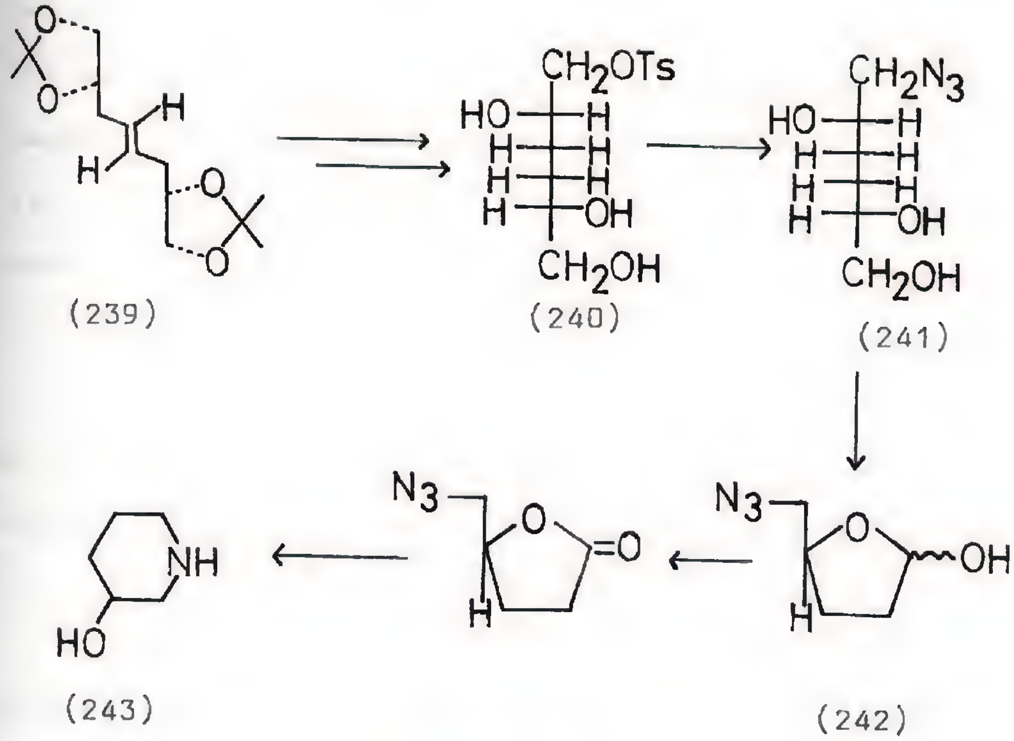
The IR spectrum of this amide (233) shows 2 carbonyl signals: one at 1770 (lactone) and the other at 1645 (amide). There is no O-benzoate signal at ca. 1720

cm^{-1}. In the PMR spectrum, the N-linked methylene protons appear as a band of signals centred at ca. δ 3.7. The same methylene carbon atom resonates at δ43.42 in the CMR spectrum (see Table 7 for complete assignment). In both NMR analysis, the presence of one benzoyl group is indicated. The most important evidence for the product (the projected N-benzoyl lactone) is due to the signal of the amide carbonyl ^{13}C resonance at δ168.29, whereas that of an O-benzoate [e.g., (229)] at 166.4. Thus all evidence suggests the identity of the product is a genuine amide, the N-benzoyl lactone (233).

(2.2.1.4) Displacement of the tosylate (242) with piperidine

The sulphonic ester (230) was refluxed with piperidine in ethanol for 5 hours, furnishing the N-piperidinium derivative (246a) (see p.125) in the form of its sulphonate salt, isolated as a gum. It was very difficult to purify. Although both the tosylate salt (246a) and the corresponding free amine (247a) produced by basification and extraction with ethyl acetate, gave spectroscopic evidence for being lactones, we sought further confirmation by passing salt (246a) through an ion-exchange resin column, Amberlite IRA410 (Cl^-), to obtain the chloride salt (246b), which was further purified by heating in aqueous solution with charcoal. After evaporation, a colourless crystalline residue was obtained, which was very hygroscopic.

The IR spectrum of this substance showed a

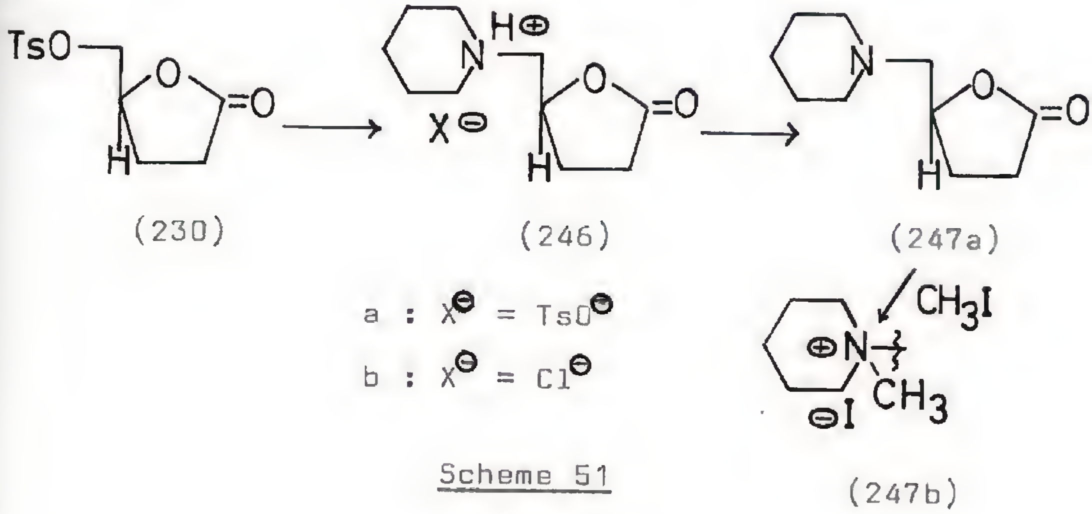


(239) (240) (241) (242) (243)

Scheme 49

(244) (245)

Scheme 50



(230) (246) (247a) (247b)

a : $X^{\ominus}$ = $TsO^{\ominus}$

b : $X^{\ominus}$ = $Cl^{\ominus}$

Scheme 51

typical ammonium stretching band (3700 to 2100 cm^{-1}) and the γ-lactone carbonyl absorption at 1770 cm^{-1}. The CMR spectrum show mainly one set of signals, which was compatible with the structure (246b) (Table 7) (see p. 121). The presence of minor signals suggested the possible presence of some of the open-chain compound.

We may note that it had not proved possible to purify the corresponding β-aminomethyl lactone to the same degree (Section 1.2.1.6).

As with the γ-aminomethyl lactone methiodide(247b), physical data suggested the presence of the quaternary salt, but purification proved too difficult to achieve.

(2.2.2) Preparation of racemic γ-aminomethyl-γ-butyrolactone salt (252) by means of iodolactonization

The use of halolactonization as means of cyclization has been mentioned in the Introduction (Section 5.1.1). The lactones thus produced are racemates. This will complement the synthesis of the optically pure isomer in the previous section.

The sequence employed in the preparation of the required γ-aminomethyl-γ-butyrolactone hydrochloride (252) is portrayed in Scheme 52

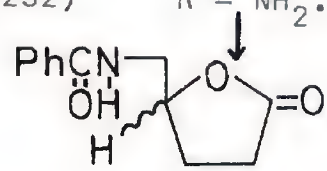
(248)

(249) R = I

(250) = (±) (229) R = $\mathrm{O\underset{\underset{O}{\|}}{C}Ph}$

(251) = (±) (231) R = N_3

(252) = (±) (232) R = NH_2.HCl



(253) = (±) (233)

Scheme 52

(2.2.2.1) Synthesis

The starting material, the iodo lactone (249), was prepared by iodolactonization of pent-4-enoic acid (248) using the method of van Tamelen and Shamma.[248] For the characterization of the iodide, the corresponding O-benzoate (250) was made. The reaction of the iodo compound (249) with benzoic acid in the presence of either potassium carbonate or triethylamine failed to cause any ester formation. However, it was possible to drive the esterification to completion by employing 18-crown-6 in the presence of anhydrous potassium carbonate in dichloromethane and refluxing the mixture for 8 hours. After purification, the benzoate (250) was obtained as

a light brown oil in 31% yield. In contrast to the more reactive allyl halides [e.g., (200)] (p.103), which had been used in the β-aminomethyl series, this reaction did illustrate the less reactive nature of the alkyl iodide (249). TLC analysis indicated considerable side-reaction occurred (giving material immobile in the solvent used), which was also reflected by the low yield.

The azide displacement was, fortunately, more successful. By heating a mixture of sodium azide and the iodo lactone (249) (see p.127) in DMF at 100° for 4 hours, the azide (251) was produced in 56%. There was strong suspicion that, especially in the presence of DMF, some of the compound (251) had been washed away, since small rather polar molecules like butyrolactones are reasonably soluble in water (also see azides of the β-series, Section 1.2.1.6). An attempt to improve the yield of the amino compound [e.g., (252)] by reacting the iodide (249) with potassium phthalimide in DMF failed. No reaction occurred at room temperature, after stirring for 2 days, whereas heating the mixture at 100° for 4 hours only gave decomposition products.

The azide (251) was reduced catalytically in an acidic medium to afford the ammonium chloride (252) in quantitative yield. The hydrochloride was derivatized as the N-benzoate (253) by the usual procedure (68% yield).

(2.2.2.2) Characterization

The series of butyrolactone derivatives (249)—(253) show the expected characteristic bands in their IR spectra.

In the ^{1}H-NMR spectra, the α and β methylene protons appear as a band of multiplets (δ2.0-2.7). The γ-methine proton shows a pseudo first-order pattern of a combination of an AB quartet and a doublet, at δ4.72 [e.g., in the amide (253)]. It will be more conveniently classified as a multiplet. The chemical shifts of the exocyclic methylene protons expectedly vary with the type of attached substituent. These non-equivalent protons form an AB quartet pattern which is further split by the methine proton to give a doublet of AB quartets with coupling constants J = 7.6 and 4.5 Hz. The PMR spectra of the iodide (249) (P-22), azide (251) (P-23), the hydrochloride (252) (P-24) and the *N*-benzoate (253) (P-25) are compiled in the Spectra Section.

The CMR spectra data are presented in Table 8 (see p.132) and also in the Spectra Section (C-22, C-23, C-24 and C-25) for the above compounds (249) and (251)—(253).

Special mention is needed to clarify the observation of the lactone and the corresponding ring-open form of the ammonium chloride (252) [see also p. 123 for the corresponding asymmetric compound (232)].

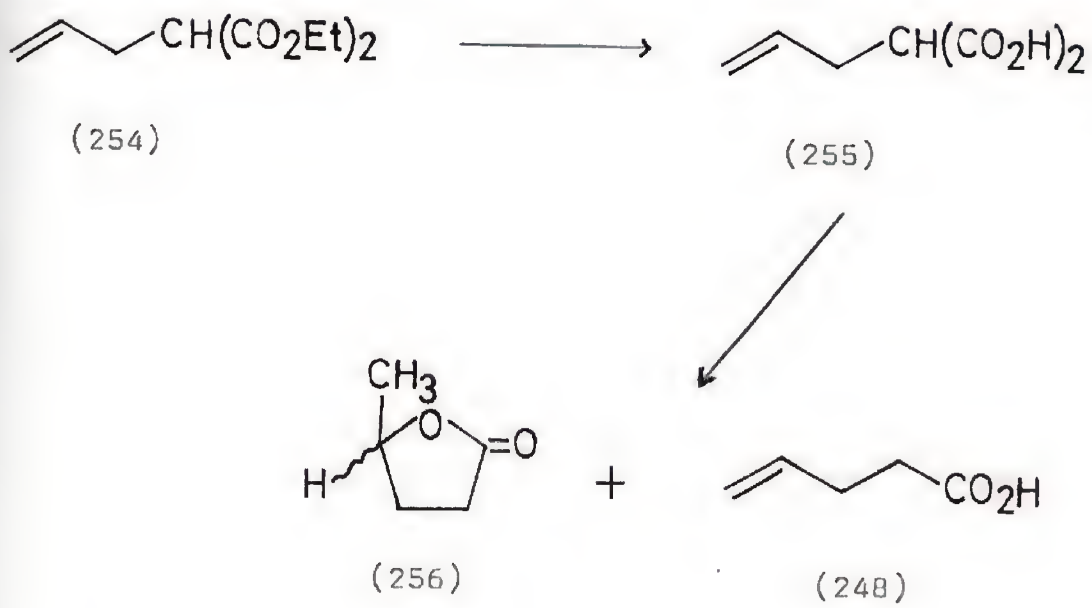
As in the chiral form (232), the amount of both the lactone and the hydrated form were measurable in the ^{13}C-NMR spectrum, judging by the relative intensity of the peaks, e.g., at δ 178.7 (lactone C=O) and 181.70 (CO_2H). In the present case, the ratio of the 2 forms was ca. 2:1. However, good yield of the benzamide (253) was also recorded (68%) from this salt, as solid. This amide (253) was the racemic form of (233). As we can see both compounds gave similar spectroscopic details [e.g., C-13 NMR measurements: Table 7 (p.121) for compound (233) and Table 8 (p.132) for compound (253)].

(2.2.2.3) Preparation of pent-4-enoic acid

Since pent-4-enoic acid [(248), see p.127], is expensive (supplied by Fluka AG at £11.6 for 5 ml.) and we were currently working on a project which needed diethyl allylmalonate (available from Aldrich Chemical Company at £8 for 100 g., a starting material for preparation of pent-4-enoic acid[249]), we made an effort to synthesize the required alkenoic acid (248).

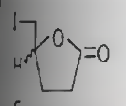
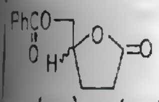
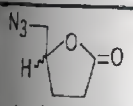
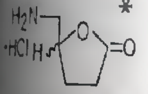
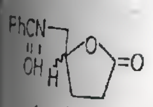
In the literature, conversion of allylmalonate (255) to (248) as in Scheme 53 by heating has been reported.[249] Thus the diacid (255) was obtained by hydrolysis of the diester (254) using sodium hydroxide. It was thought the acidification and heating the very acidic aqueous solution (refluxing temperature for 1.5 hours) should induce decarboxylation. However, after

work-up, only the diacid (255) was produced. After isolation, the diacid was suspended in 6N aqueous hydrochloric acid and heated at 160-170^{o} in an oil bath for one hour. This time a lactone was formed in quantative yield. On examination of the NMR spectrum, it was shown that this compound was the γ-valerolactone (256). Apparently, under these more stringent conditions, not only did decarboxylation occur, intramolecular cyclization was enhanced as well. Thus the literature procedure was followed by heating the solid (255) in an oil-bath at 150^{o}. The solid melted with effervescence. (It was also noticed that when the melting point was taken, decarboxylation occurred). After 30 minutes the resulting light brown oil was checked by TLC and NMR spectroscopy. It was found that the product was a mixture of the required acid (248) and some 25% of the ring-closed isomer (256). The product-



Scheme 53

Table 8 : CMR spectral data of some racemic γ-substituted γ-lactones

Compounds	Solvent	C-1	C-2	C-3	C-4	C-5	Other carbons
 [(249),(±)-form]	$CDCl_3$	176.48	28.84	28.12	78.58	7.48	
 (250)=(±)(229)	$CDCl_3$ (200 MHz)	176.54	28.17	23.97	77.46	65.72	128.53, 129.44,(aromatic) 129.67 & 133.38,166.09(ester)
 (251)=(±)(231)	$CDCl_3$	176.75	28.25	24.60	78.25	54.23	
*  (252)=(±)(232)	D_2O + 1,4-dioxand	178.70	29.62	28.58	78.58	43.55	
 (253)=(±)(233)	$CDCl_3$	177.67	28.65	24.87	79.82	43.55	127.47, 128.78, 132.03 & 134.2 (aromatic) 168.65 (amide)

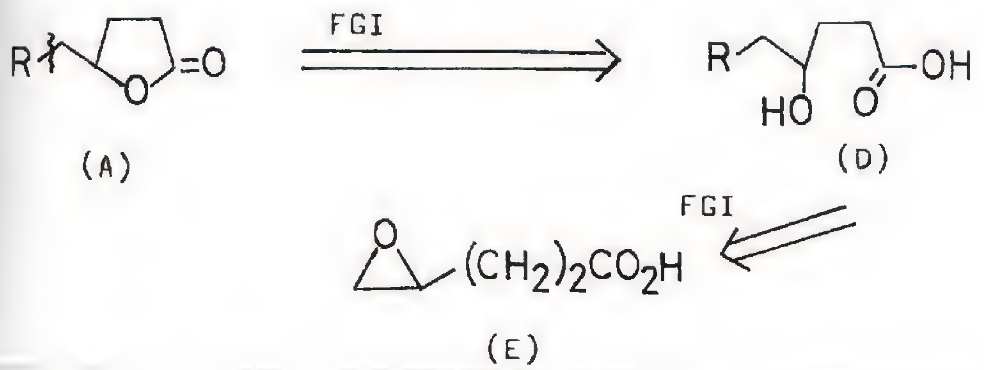
* Footnote :

Perhaps due to solvent change, the ^{13}C readings of racemic salt (252), using D_2O + 1,4-dioxane as solvent and standard, are different from those of the chiral compound (232), using D_2O + DSS as solvent and standard (Table 7, see p.121).

ion of the lactone may be due to self-catalyzed cyclization because of the acidic nature of the carboxylic acid and also of the application of high temperature. This is obviously why the commercial product, which has been purified by distillation, is so expensive.

The lactone (256) could be recognized in its PMR spectrum by the distinctive doublet (methyl group) at $\delta 1.4$ and the vicinal lactonic methine proton with which it is coupled, appearing as a multiplet at $\delta 4.6$. This compound was spectroscopically identical to γ-valerolactone.[250]

(2.3) Synthesis by way of (b)-disconnection



As explained in the β-aminomethyl series (Sections 1.2 and 1.5), it is difficult to mark out a clear-cut division between this disconnection from the (a)-disconnection, except that this time the construction of the amino equivalent is done before the formation of the γ-butyrolactone ring.

(2.3.1) Epoxidation of diethyl allylmalonate

The utility of oxiranes [e.g., (257) see p.136] as intermediates in synthetic chemistry has been widely studied.[251] There are also numerous procedures applicable to the preparation of epoxides.[252] Peracid oxidation of alkenes is perhaps the most well-established method.[253] Recently , other reagents have been introduced[254] (including molecular oxygen[254a] and sodium hypochlorite in the presence of manganese porphyrin[254b]).

The highly strained cyclic oxide can be transformed into various organic compounds by a ring opening reaction. For example, nucleophilic attack by a carbanion gives mainly a secondary alcohol.[251,255] Oxiranes have been converted regiospecifically into primary alcohols *via* reaction with organotin derivatives.[256]

The sequence used in this work is given in Scheme 54 (p.136).

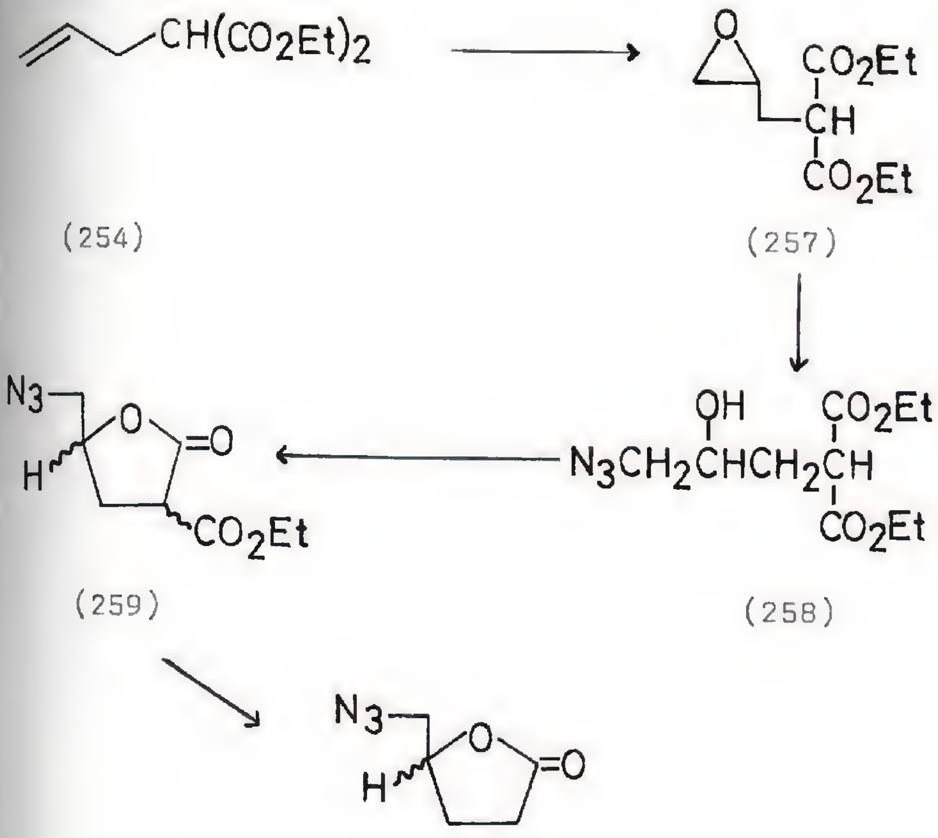
(2.3.1.1) Synthesis

The required epoxide (257) was prepared by the reaction of the alkene (254) with *m*-chloroperbenzoic acid (MCPBA). The use of 1.2 equivalents of the peracid for 4-7 hours (at ambient temperature) gave only partial reaction, so a large excess of MCPBA (5 equivalents) was used for 2 days. The required epoxide (257) was obtained in 97% yield. Partially oxidized mixture was retreated

with peracid for a further period to afford the fully epoxidized product.

The synthesis of this epoxide (257) has been achieved[257] by the use of peracetic acid. In this paper, the amount of oxidant used is not specifically mentioned; the reaction was carried out at about 30^{o} for one day.

Reaction of the epoxide (257) with sodium azide in ethanol gave the azido alcohol (258) by substitution at the primary carbon. However, after work-up involving dilute acid washing, the corresponding lactone (259) was obtained. On examination of the PMR spectrum of the product, it was discovered that the ethyl group signal integration was too low. Therefore, we concluded that some of the lactonic ester (259) decarboxylated during the isolation process. Presumably, this lactonic ester is easier to decarboxylate than that of the *gem*-dicarboxylic acid (255). Thus it was decided to bring the reaction through to the azide (251) as in a one-step synthesis starting from the epoxide (257). The mixture of (259) and (251) was heated in dilute hydrochloric acid solution to effect complete decarboxylation to give just the azido lactone (251). After purification, the product was obtained in 39% overall yield, which was identical to the authentic azide prepared previously (spectroscopic and TLC analysis).

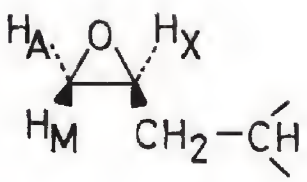


(251) = (±) (231)

Scheme 54

(2.3.1.2) Characterization

The structure elucidation of the oxirane (257) is by infrared, ^{1}H NMR and ^{13}C NMR spectroscopies. The strong ester carbonyl absorption peak is visible at 1720 cm^{-1}. The PMR spectrum shows the epoxide protons as an AMX pattern to a first order approximation.



H_M, at δ2.54 as doublet of doublets $\underline{J}_{(A,M)} = 5$ Hz and $\underline{J}_{(M,X)} = 2.7$ Hz;

H_A, at δ2.8 as doublet of doublets $\underline{J}_{(A,M)} = 5$ Hz, and $\underline{J}_{(A,X)} = 4$ Hz;

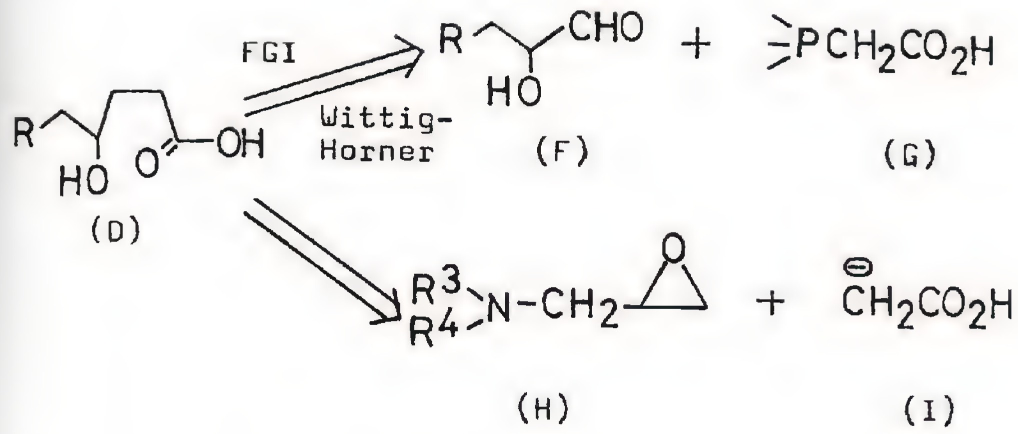
H_X, at δ3.04 as multiplet due to the coupling as in the X part of an AMX spectrum and also coupled to methylene protons.

A doubling of the ethyl signals can also be observed, one for each group. The full spectrum appears in P-27 (Spectra Section). In the CMR spectrum, only one set of signals for the ethyls and for the carbonyls is observed. The epoxide carbon atoms resonate at δ49.15 and 49.93 assigned to primary and secondary carbon respectively. (Spectrum C-27).

The lactonic ester (259), showed infrared absorption as expected, whereas peaks were clearly seen for the azide, γ-lactone and ester carbonyl groups (at 2100, 1770 and 1720 cm^{-1} respectively). The PMR spectrum showed the expected absorptions, including a band of multiplets for the γ-lactone protons (at δ2.58-2.78) and a multiplet assigned to the azide methylene protons.

The decarboxylation product (251) provided identical spectral data to those obtained by the previous route (Section 2.2.2).

(2.4) Synthesis by means of (c)-disconnection



In this construction, acetic acid derivatives are required to react with an aldehyde or an epoxide. The chain extension is provided by (1) a Wittig-Horner reaction and (2) epoxide ring opening by the synthon for $^{\ominus}CH_2CO_2H$.

(2.4.1) Preparation of the chiral building block (S)-4-hydroxymethyl-γ-butyrolcatone (228)

In parallel with the synthesis of this alcohol (228) from an amino-acid (L-glutamic acid, see p. 115), the use of a carbohydrate precursor in the manufacture of this same compound is reported here (see p.143 for reaction scheme).

The synthesis of this chiral alcohol (228) or its precursor [e.g., (261)] from glyceraldehyde [(260),

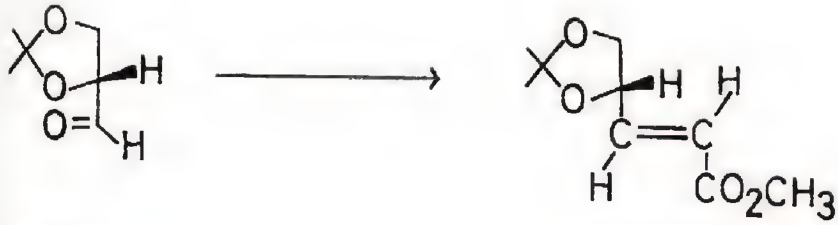
see p.140][258] or the related iodide (262)[259] or oxirane (264)[243b] by various chemical transformations has been reported (Scheme 55). The reaction of 2,3-isopropylidene-D-glyceraldehyde (260) with Wittig reagents (using ylides)[258a,b] or using the Knövenagel-Doebner reaction with active methylene compounds[258c] (e.g., malonic acid) can give α,β-unsaturated acids or esters [e.g., (261)]. The iodide (262)[259] or epoxide (264)[243b] reacts with diethyl sodiomalonate to afford (228) after further manipulation.

(2.4.1.1) Synthesis of 2,3-isopropylidene-D-glyceraldehyde (260)

The starting material for the preparation of the aldehyde (260) was 1,2 : 5,6-di-O-isopropylidene-D-mannitol (266) which was prepared from D-mannitol by the method of Chittenden.[260] There was also some of the tris-acetalated product (267) formed, which could be separated from (266) by column chromatography.

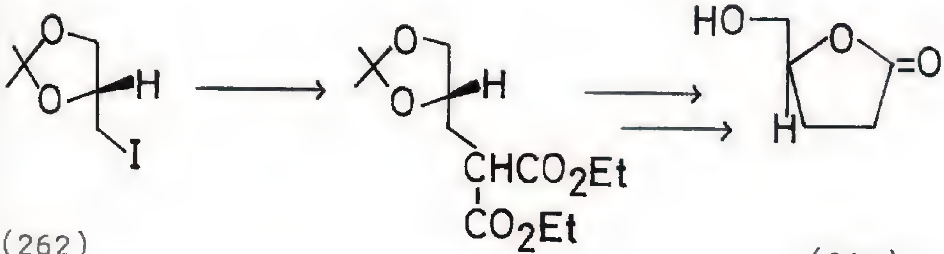
Glycol cleavage of the diol (266) by either sodium metaperiodate[261] using phase-transfer conditions[243b] or lead tetraacetate[262] gave the aldehyde (260). In the infrared spectrum, a hydroxyl signal (at 3420 cm^{-1}) and a carbonyl absorption peak (at 1735 cm^{-1}) could be observed and the ^1H-NMR spectrum was much more complex than that expected of the pure glyceraldehyde (260). Apparently this was a mixture of the aldehyde and some

(A)



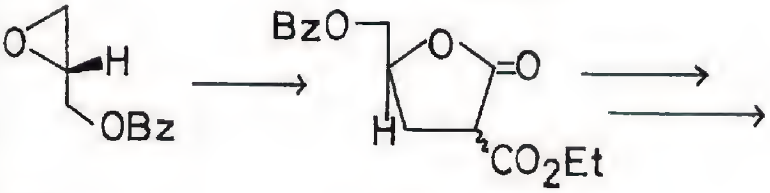
(260) (261)

(B)



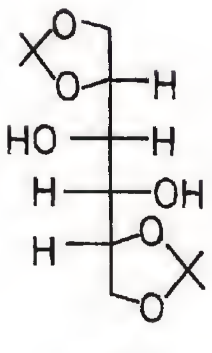
(262) (263) (228)

(C)

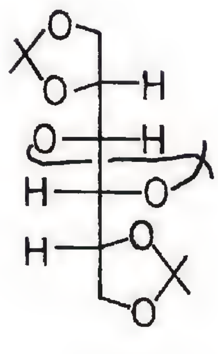


(264) (265)

Scheme 55



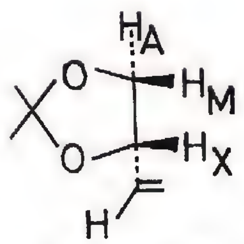
(266)



(267)

of its hydrate. It is known that some aldehydes appear in dimeric or polymeric form and this also explains the

presence of hydroxyl groups (e.g., ethyl glyoxylate derived from periodic acid cleavage of tartaric acid diester[263]). To prove the identity of the oxidation product, the above prepared aldehyde (260) was converted to its 2,4-dinitrophenylhydrazone (268) (see p.143) by the standard procedure (see Experimental Section). Interestingly, this isopropylidene glyceraldehyde hydrazone (268) has not been reported but only the corresponding deacetonated compound. The orange yellow crystals have a melting point of 83^o. The PMR spectrum of (268) shows two clear 3-proton singlets for the 2 methyls, at δ1.38 and 1.42. Like the epoxide [(257), see p.136], the 3-protons of the 1,3-dioxolane ring appear in an AMX pattern.



H_M, at δ4.03 as doublet of doublets, $\underline{J}_{(A,M)}$ = 8 Hz and $\underline{J}_{(A,X)}$ = 6 Hz;

H_A, at δ4.28 as doublet of doublets, $\underline{J}_{(A,M)}$ = 8 Hz and $\underline{J}_{(M,X)}$ = 6 Hz;

H_X, at δ4.78 as well-balanced AB quartet, perhaps a combination of couplings with H_A, H_M and the "aldehydic" H, $\underline{J}$ = 6 and 13 Hz;

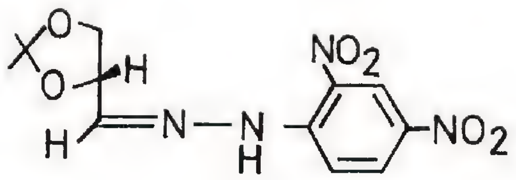
H , at δ8.98 as doublet, $\underline{J}$ = 3 Hz (also see Spectrum P-28).

In the ^{13}C-NMR spectrum, the dioxolane ring carbons give signals at δ66.8, 75.07 and 10.97, and the aldehydic carbon at δ151.04 (Spectrum C-28).

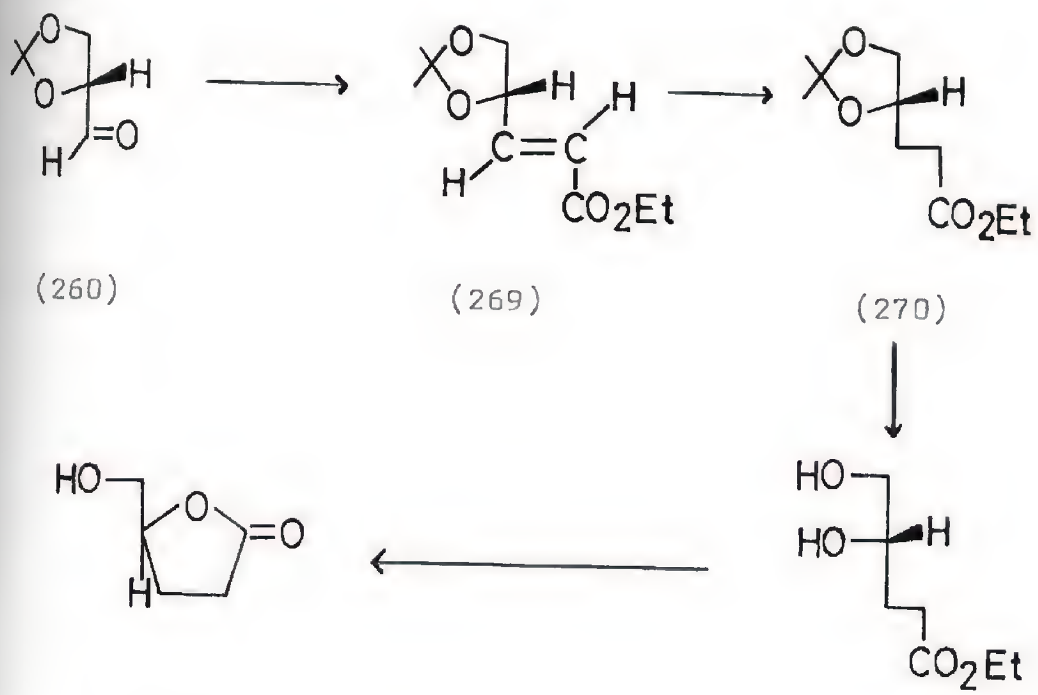
(2.4.1.2)Synthesis of the unsaturated ester (269) and 4-hydroxymethylbutyrolactone (228)

As mentioned before, although the methyl ester of the α,β-unsaturated acid (261) (p.140) has been prepared by either a Wittig reaction[258a,b] or a Wittig-Horner reaction[258a] and the ethyl ester (269) (see p.143) (one of the two isomers) by a Knövenagel-Doebner reaction,[258c] the synthesis of this ester (269) by the Wittig-Horner methodology has not been reported. Furthermore, the conversion of this to (228) (Scheme 56) has not been tried.

The Wittig-Horner reaction was conducted as for 1,3-diacetoxypropanone (109) (see Discussion, Section 1.2.1.2) (p.55). However, only a fair yield (ca. 50%) of the α,β-unsaturated ester (269) was obtained. Perhaps, there was a chance of further polymerization of the aldehyde by the presence of a strong base, sodium hydride. It was noticed that a good deal of organic solid was also formed during the reaction. Recently, a procedure for the Horner-Wadsworth-Emmons reaction for base-sensitive compounds has been published by Masamune.[264] The method might have been useful for this preparation. However, the project was terminated before this paper appeared.



(268)

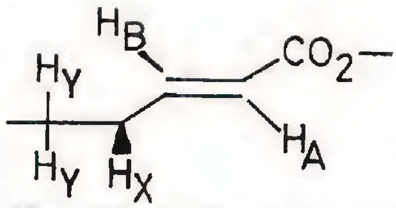


(260) (269) (270)

(228) (271)

Scheme 56

The spectroscopic data of (269) correlated well with those of the reported trans-α,β-unsaturated ester prepared by the Knövenagel-Doelner reaction.[258c] The stereochemistry of (269) about the double-bond is trans as indicated by ^{1}H-NMR spectroscopy. In the PMR spectrum, an ABX system is observed for the olefinic protons (A and B) and the dioxolanyl proton (X).



H_X shows further coupling to the other protons in the dioxolanyl ring. H_B appears at $\delta 7.0$, $J_{(A,B)} = 20$ Hz, $J_{(B,X)} = 8$ Hz, and H_A at $\delta 6.5$, $J_{(A,X)} = 2.6$ Hz, $J_{(A,B)} = 20$ Hz. H_X resonates at $\delta 4.70$, as a combination of triplet and doublet of doublets, $J_{(X,Y)} = 7.8$ Hz, $J_{(X,B)} = 8$ Hz, $J_{(X,A)} =2.6$ Hz run on a 60-MHz NMR spectrometer (Spectrum P-29). These couplings are comparable with those of methyl trans-manno-octenoate prepared by a Wittig reaction.[265] The ^{13}C-NMR spectrum is also consistent with the assigned structure of (269) (Spectrum C-29).

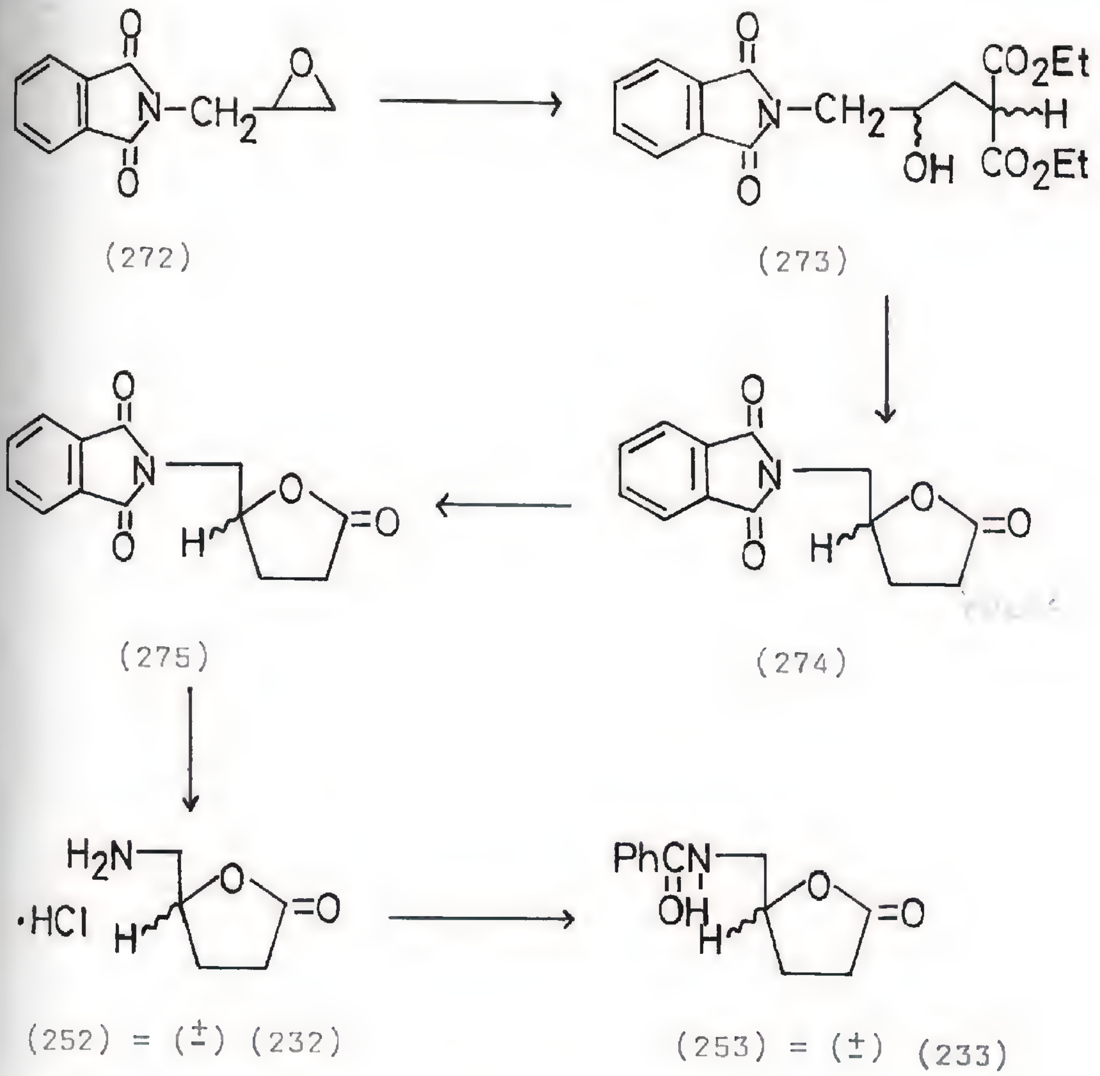
The α,β-unsaturated ester (269) was hydrogenated with 10% palladium-on-charcoal as catalyst. However, spectral analysis suggested the product to be a mixture of the hydroxy ester (271) (p.143) and hydroxy lactone (228). The starting ester (269) was apparently absent since no isopropylidene signal could be observed in the ^{1}H-NMR spectrum of this mixture. The mixture was therefore treated with trifluoroacetic acid to give the chiral hydroxymethyl lactone (228), which was spectroscopically identical to the one prepared from L-glutamic acid.

(2.4.2) Preparation of racemic 4-amino-methyl-γ-butyrolactone salt (252)

The starting material for this series of reactions is a functionalized epoxide [e.g., (272)], with the two carbon unit drawn, conveniently, from diethyl malonate.

Nucleophilic ring opening of the phthalimido epoxide (272), for example, with water, ammonia and other amines, has been reported,[266] but no reactions with carbanions have been found in the literature.

The reaction of the epoxide (272) with diethyl sodiomalonate should furnish the hydroxy ester (273). After work-up, in line with the results in the previously discussed reaction using diethyl malonate, a mixture of the lactonic ester (274) and the lactone (275) was obtained. It was decided to complete the decarboxylation by refluxing the mixture with dilute hydrochloric acid. However, TLC analysis indicated that the phthalimido protecting group was being removed simultaneously with the decarboxylation. The phthalic acid liberated was removed by extraction. From PMR and TLC evidence, there was still a small amount of the carboxylic acid left even after several washings. The diastereomeric ammonium chloride (252) (see p.146 for synthetic scheme) was further derivatized as its N-benzoate (253), which had been fully characterized as the required amide.



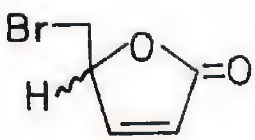
Scheme 57

The discovery that dilute hydrochloric acid can be used to deprotect phthalimido compounds may prove to be useful for the elaboration of β-phthalimidomethyl-Δ^2 -butenolide (203) (Section 1.5, see p.102).

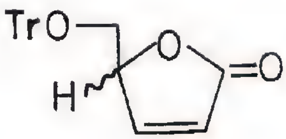
(2.5) Some useful candidates for the transformation to γ-aminomethyl-γ-lactones

The synthesis of several 2-butenolide intermediates [e.g., (276)-(278)] has been reported by Font[267] from either glyceraldehyde or n-butoxymethyloxirane. Some enantiomerically pure $\Delta^{\alpha,\beta}$-butenolides [e.g., (279) and (280)] have also been prepared by the Spanish group[268] by functionalizing the product from pyrolysis of 2,3-O-isopropylidene-D-ribono-γ-lactone (281).

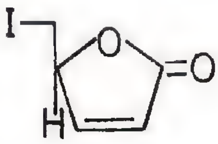
(276)



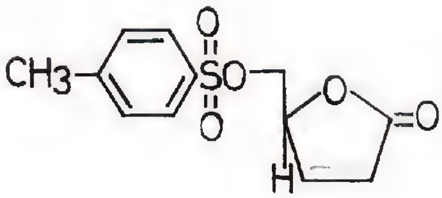
(277)



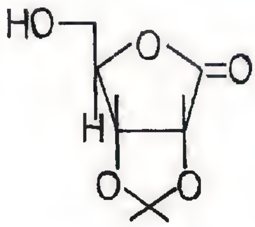
(278)



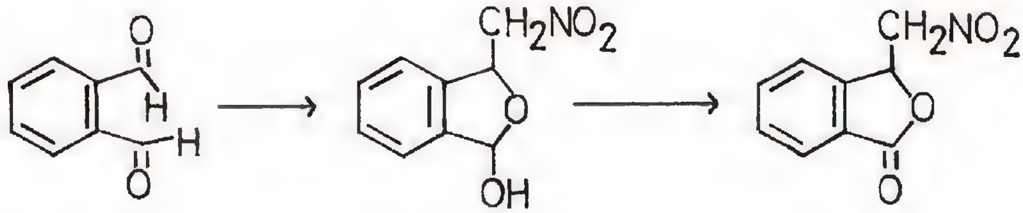
(279)



(280)



(281)



(282) (283) (284)

Scheme 58

Another valuable intermediate is the 3-nitromethylphthalide (284), which, for example, has been made by the Henry addition of nitromethane to O-phthaldehyde (282) and followed by the oxidation of the adduct (283)[269] (Scheme 58). The pharmacology of the corresponding ammonium chloride[98b,c] has been mentioned in the Introduction (Section 4).

(3) Preparation of the α-aminomethyl-γ-butyrolactones by direct functionalization of preformed lactones

α-Aminomethylbutyrolactones [e.g., (308a)] are not exactly structural analogues of GABA unlike β-aminomethylbutyrolactone (120); however, they are lower analogues.

The synthesis was performed in either of two ways: (a) using the enolate anion of the γ-lactone as a nucleophile, where the transformation (303)→(305) (Scheme 62) (see p.153) has not previously been reported; (b) by displacing the bromine of an α-bromo-γ-lactone with a carbon nucleophile, such as cyanide ion (180)→(306) (Scheme 63) (p.158). However, α-cyanobutyrolactone (306) is a known compound (by reacting ethyl cyanoacetate with ethylene oxide in the presence of a base) which has been reported in 1940;[270] but it has not been studied recently.

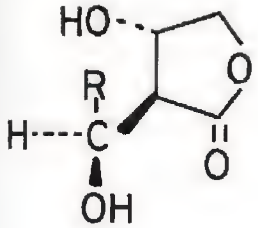
(3.1) Utilization of the acidic α proton of a γ-butyrolactone

Lactones can be substituted in the α-position by conventional reactions involving intermediate enolate anion. For example, Aldol reaction of lithium and other metal enolates of 3-hydroxybutyrolactone with aldehydes can give a mixture of the erythro and threo isomeric alcohols[271] [e.g., (285) and (286), respectively] (p.151)

α-Acyl derivatives (287) are produced by Claisen condensation[272] of γ-lactones with carboxylic esters in the presence of sodium methoxide. Treatment of saturated lactones with tris(dimethylamino)methane,[273a] Brederick's reagent [[$(CH_3)_2N]_2CHO$-*t* Bu],[273b,c] or Gold's reagent [$(CH_3)_2N$-CH=N-CH=$N^+(CH_3)_2Cl^-$],[273d] affords an α-(dimethylaminomethylene) compound [*e.g.*, (288)]. The use of Eschenmoser's salt [$CH_2=N^+(CH_3)_2I^-$] can provide a dimethylamino derivative (289) *via* the α-carbanion of the lactone[274a] (144)→(289) (Scheme 59). This amino lactone (289) has also been prepared by the reaction of α-bromo-γ-butyrolactone with Eschenmoser's salt promoted by zinc-graphite[274b] and also by the reductive amination of α-hydroxymethylene-γ-butyrolactone sodium salt[274c] (296)→(289) (as in Scheme 62, see p.153).

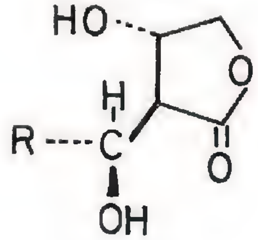
The anti-inflammatory enamines (292) have been synthesized[275] directly from the tetronic acids (290) or *via* the formyl compound (291) (Scheme 60) (p.152) by reacting with dimethylformamide acetal or with dimethoxymethyl acetate, respectively. β,γ-Butenolide (293) can react with an ynamine such as (294) to afford the corresponding adduct (295)[276] (Scheme 61).

The Claisen condensation with ethyl formate was conducted as reported[277] to give the "salt" (296) of the corresponding enol in high yield (81%). The isolated product is mainly in the form of the enol (297) rather than the aldehyde (298). It was possible to see the



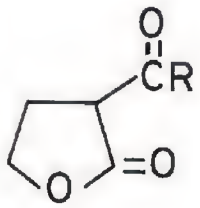
Erythro

(285)

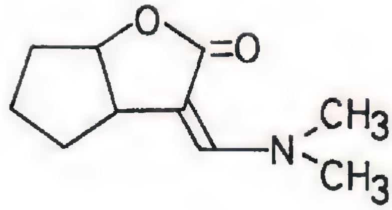


threo

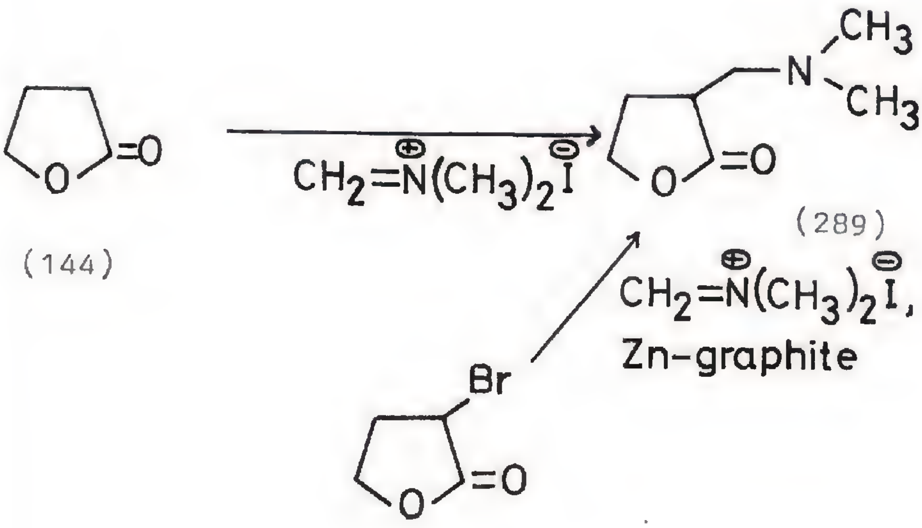
(286)



(287)

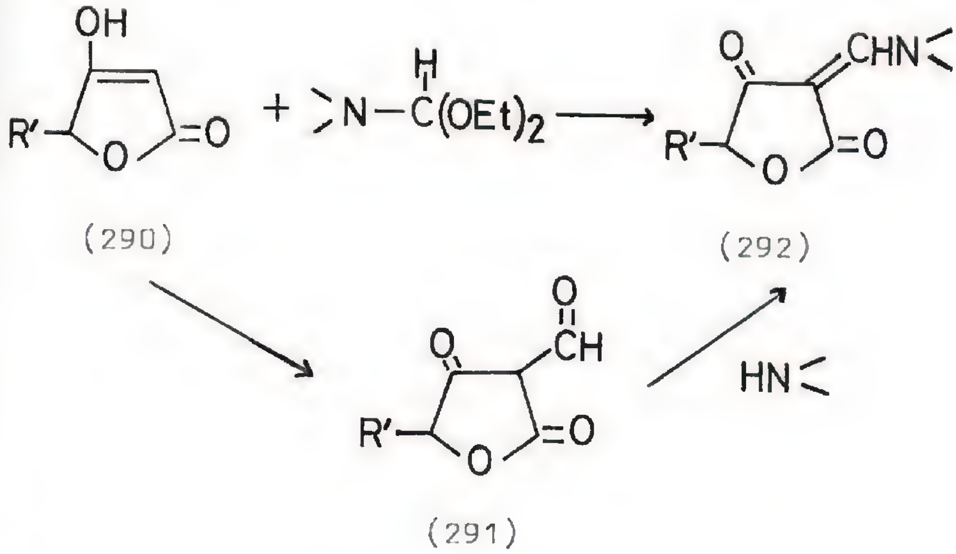


(288)



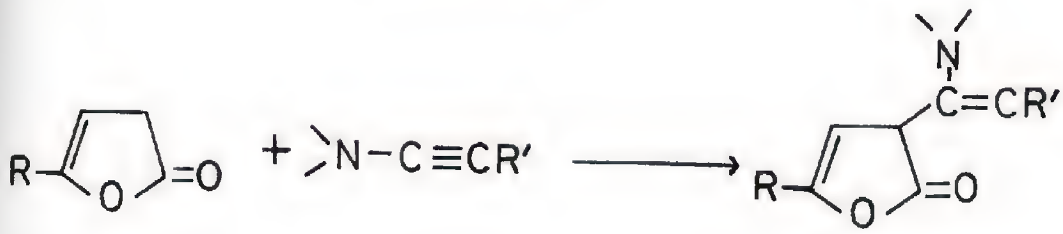
(144) (289) (180)

Scheme 59



(290) (292) (291)

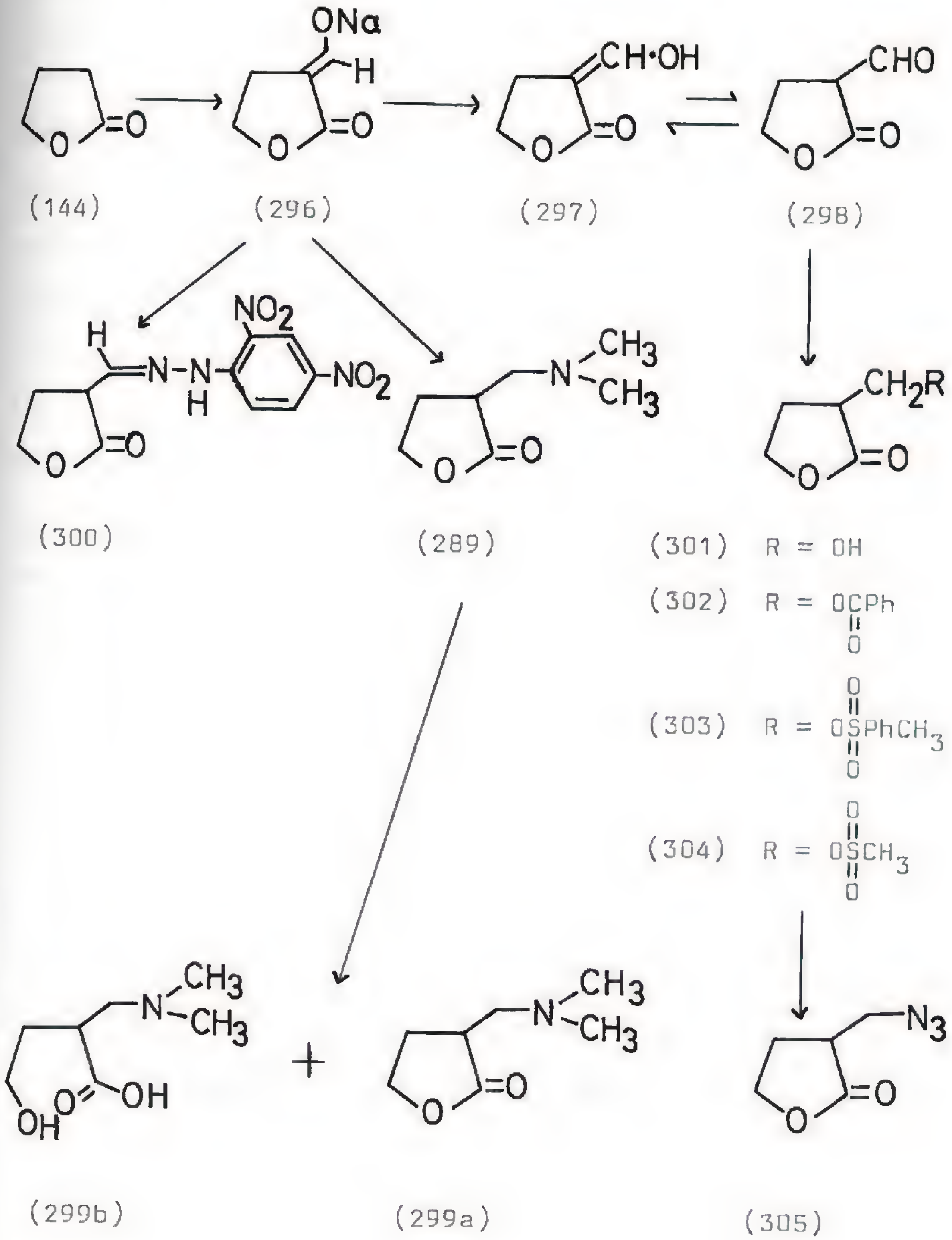
Scheme 60



(293) (294) (295)

Scheme 61

presence of both isomeric structures in the ^{1}H-NMR spectrum of the product (measured in D_2O), with a ratio of ca. 3:1 in favour of the enolic form. (Presumably, the product of the reaction was not the salt, but free enol). To characterize the compound (296), the corresponding 2,4-dinitrophenylhydrazone (300) was obtained by a conventional procedure, but first adding one equivalent of acetic acid to liberate the free enol/keto tautomers, besides adding a few drops of the acid as catalyst. Satisfactory physical data could be produced for the resulting hydra-


ONa
H
CH·OH
CHO
(144)
(296)
(297)
(298)
NO_2
H
N-N
H
$-NO_2$
CH_3
N
CH_3
CH_2R
(300)
(289)
(301) R = OH
(302) R = OCPh
(303) R = OSPhCH$_3$
(304) R = OSCH$_3$
CH_3
N
CH_3
OH
OH
+
CH_3
N
CH_3
N_3
(299b)
(299a)
(305)

Scheme 62

zone (300).

The reductive amination of (296) with dimethylammonium chloride in the presence of sodium borohydride furnished a mixture of products, including some of the required dimethylamino lactone (289). However, using the reported reducing agent,[277] sodium cyanoborohydride, a fair yield of the amino lactone (289) could be obtained. It is known that $NaBH_3CN$ has been successfully applied to reduce imines and the yields are far better than those using other general reducing agents. Treatment of the amine (289) with concentrated hydrochloric acid afforded a white solid, the ammonium chloride (299). This salt had very similar physical properties to that reported[277] (data including IR, 200 MHz-PMR and melting point). However, we noticed, in the ^{13}C-NMR spectrum of (299), the lactone (299a) and open-chain form (299b) were observed [as in the γ-aminomethyl series (see p.123 and 129)], in a ratio of roughly 2:1, as indicated by the relative intensity of the peaks.

The reduction of the formyl (or hydroxymethylene) group with sodium borohydride, either as the salt (basic solution)[278] or, after neutralization with dilute hydrochloric acid, as the aldehyde (298), gave the desired alcohol (301) in ca. 55% yield. We preferred to use the latter method, which did produce a slightly purer sample. The IR and NMR spectra of the compound (301) are consistent with its assigned structure. The alcohol (301) has

also been prepared by hydrogenation of the aldehyde (298)[279a] or the sodium salt (296).[279b] Another synthesis of the α-hydroxymethyl-γ-butyrolactone (301) has been reported[279c] by the reaction of 2-butenolide with methanol in the presence of t-butyl peroxide $(Me_3CO)_2$, as a mixture of (301) and its β-isomer, in ca. 40% yield. The structure of the lactone was further confirmed by benzoylating the alcohol to the corresponding ester (302) in 53% yield after chromatographic purification. The infrared spectrum of this benzoate (302) shows 2 diagnostic carbonyl peaks: γ-lactone (1770 cm^{-1}) and ester (1720 cm^{-1}). The ^1H NMR spectrum is more complex due to the extensive couplings of the ring protons, even at 200 MHz. However, it is possible to analyzye the exocyclic methylene protons. A doublet of AB quartets is recognized at δ 4.58 and 4.77 with coupling constants: J = 5.8 and 4 Hz (see Spectrum P-30). In the CMR spectrum the carbon atoms of the γ-lactone resonate at δ 176.7, 39.4, 25.9 and 66.8 (Spectrum C-30).

Tosylation of the alcohol (301) gave a solid in low yield (16%), which was spectroscopically characterised as the sulphonate ester (303). However, when azidolysis was performed on this sulphonate in DMF, no azide (305) was obtained, only decomposition occurred. Perhaps this could be rationalized by the fact that the very reactive tosylate (303) might readily undergo elimination (azide ion acting as a base) to the (exo)methylene-γ-butyrolactone which could then degrade easily.

This could also account for the low yield of the isolated sulphonate. As an alternative, the mesylate (304) was prepared by a standard procedure. Even though there was evidence that the sulphonate did form, purification proved to be difficult. Thus, without further purification, it was treated with azide but using a different solvent system (aqueous acetone). We hoped that the use of the rather less reactive mesyl ester would improve the yield of azide (305). On TLC analysis, a new spot was detected, but the growth of the baseline product was even faster. When all the mesylate (304) had been consumed, the required product was purified by column chromatography. The IR spectrum of the azide (305) showed the characteristic azide band at 2100 cm^{-1} (but comparatively weaker than that of the carbonyl signal). However, the ^{1}H-NMR and C-13 NMR spectra showed the product to be a gross mixture. As stated before, decomposition was likely with such activated systems. The use of sulphonic acid esters as intermediate for the α-methylenation of lactones has been reviewed.[128e,f]

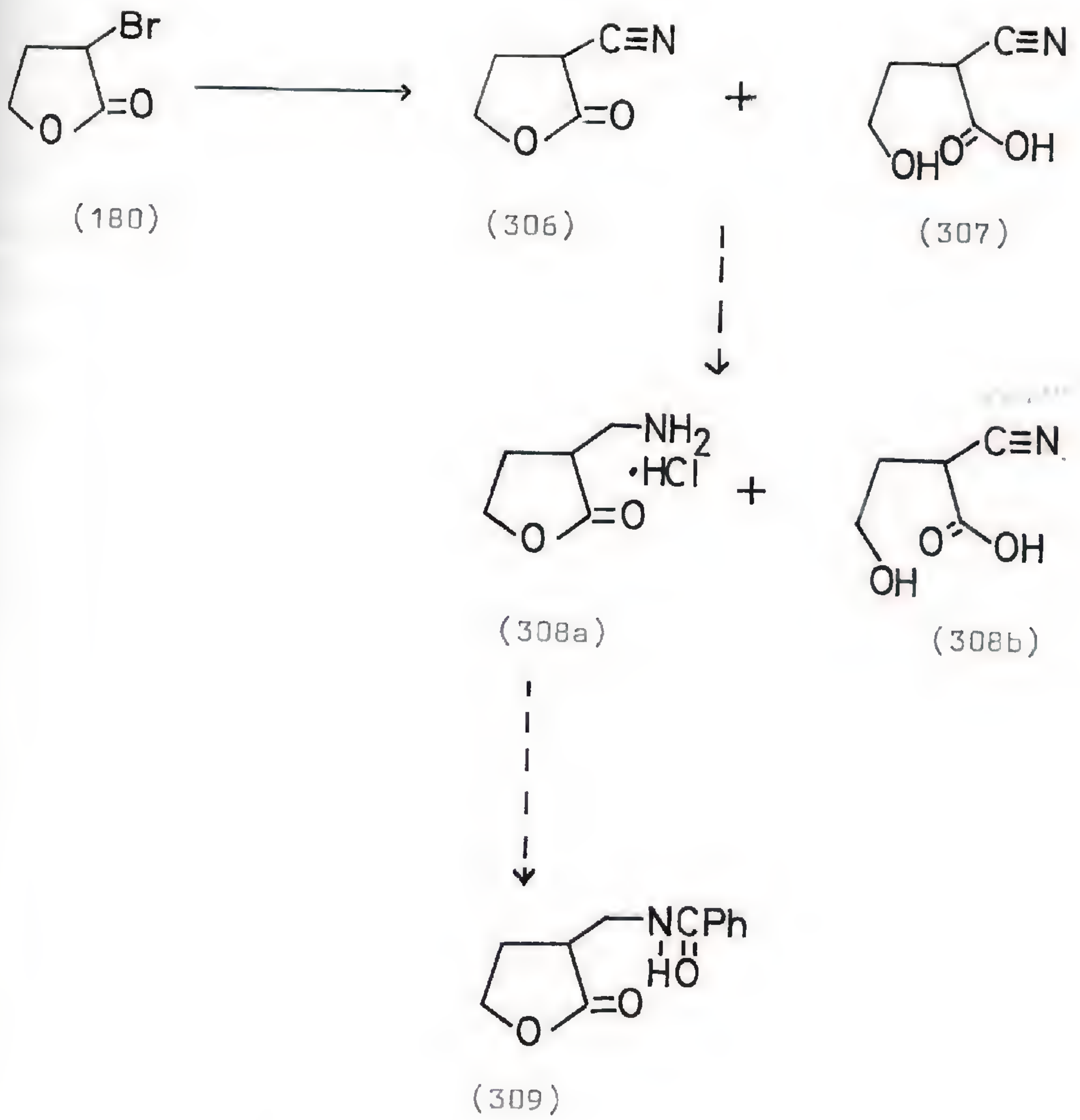
(3.2) Nucleophilic displacement of α-bromo-γ-butyrolactone with cyanide ion

The reaction between cyanide ion and alkyl halides represents a convenient method for the preparation of nitriles.[280] Primary halides give good yields of nitriles; secondary halides give low yields. The reaction fails for tertiary halides, which give elimination under these

conditions. Many other functional groups on the molecule do not interfere (of course, except the competitive ones). This is an important way of increasing the length of a carbon chain by one carbon: nitriles are easily hydrolyzed to carboxylic acids and can also be reduced to aminomethyl groups.[281] The cyanide ion is an ambident nucleophile, and isonitriles may be side products.

Although α-bromo-γ-butyrolactone (180) may be expected to function as a secondary alkyl halide, there are two sites in the molecule which can undergo nucleophilic attack, namely: the bromide and the lactone functional group. Both the bromide and the carboxylate ion are relatively good leaving groups.

The reaction of α-bromo-γ-butyrolactone (180) (see p.158) with sodium cyanide in DMF by stirring at room temperature for 3 days gave a mixture of the lactone (306) and its hydrated form (307). IR spectrum of the product revealed the presence of the broad OH group (ca. 3500 cm^{-1}), 2 carbonyl signals at 1770 cm^{-1} (lactone C=O) for compound (306) and 1720 cm^{-1} (carboxy C=O) for the acyclic form (307). Duplicated peaks were observed in the ^{13}C-NMR spectrum, for instance, at δ 115.88 and 116.14 (two signals for C≡N), δ169.5 (CO_2H) and δ173.82 (lactone C=O). The above evidence (IR and CMR) strongly supported the proposed mixture of the product. Judging by the relative intensity of these 2 sets of peaks, the ratio of the lactone (306) to the acid (307) was 3:2.



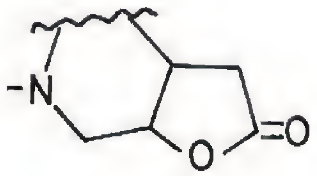
Scheme 63

Hydrogenation of the mixture [(306) and (307)] over palladium-on-charcoal[282] gave a compound [assumed as a mixture of the ammonium chloride (308a) and the acyclic acid (308b)]. However, N-benzoylation of this mixture failed to deliver the desired benzamide (309) and hence the presence of (308a) in the product of hydrogenation could be excluded.

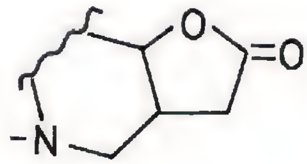
(4) <u>Aza-heterocycles as part of bicyclic γ-butyrolactones</u>

As mentioned in the Introduction (p.15), aza-heterocycles can also be regarded as analogues of GABA and show interesting neurological activity. We have attempted to prepare fully saturated azaheterocycles to extend these studies and relate such derivatives to the monocyclic butyrolactones we have prepared.

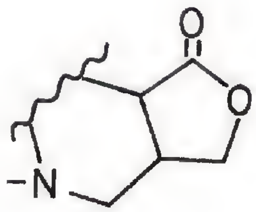
We have tried to make saturated azoles and azines, which contain the part structures (A)-(D) shown below.



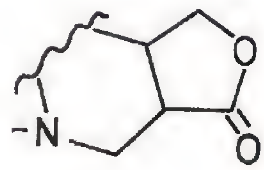
(A)



(B)



(C)



(D)

By comparison with the α-, β- and γ-aminomethyl-γ-butyrolactones, the above structures (A)-(D) can be classified as:-

(1) resembling γ-aminomethyl-γ-butyrolactone: (A) belongs to this category;

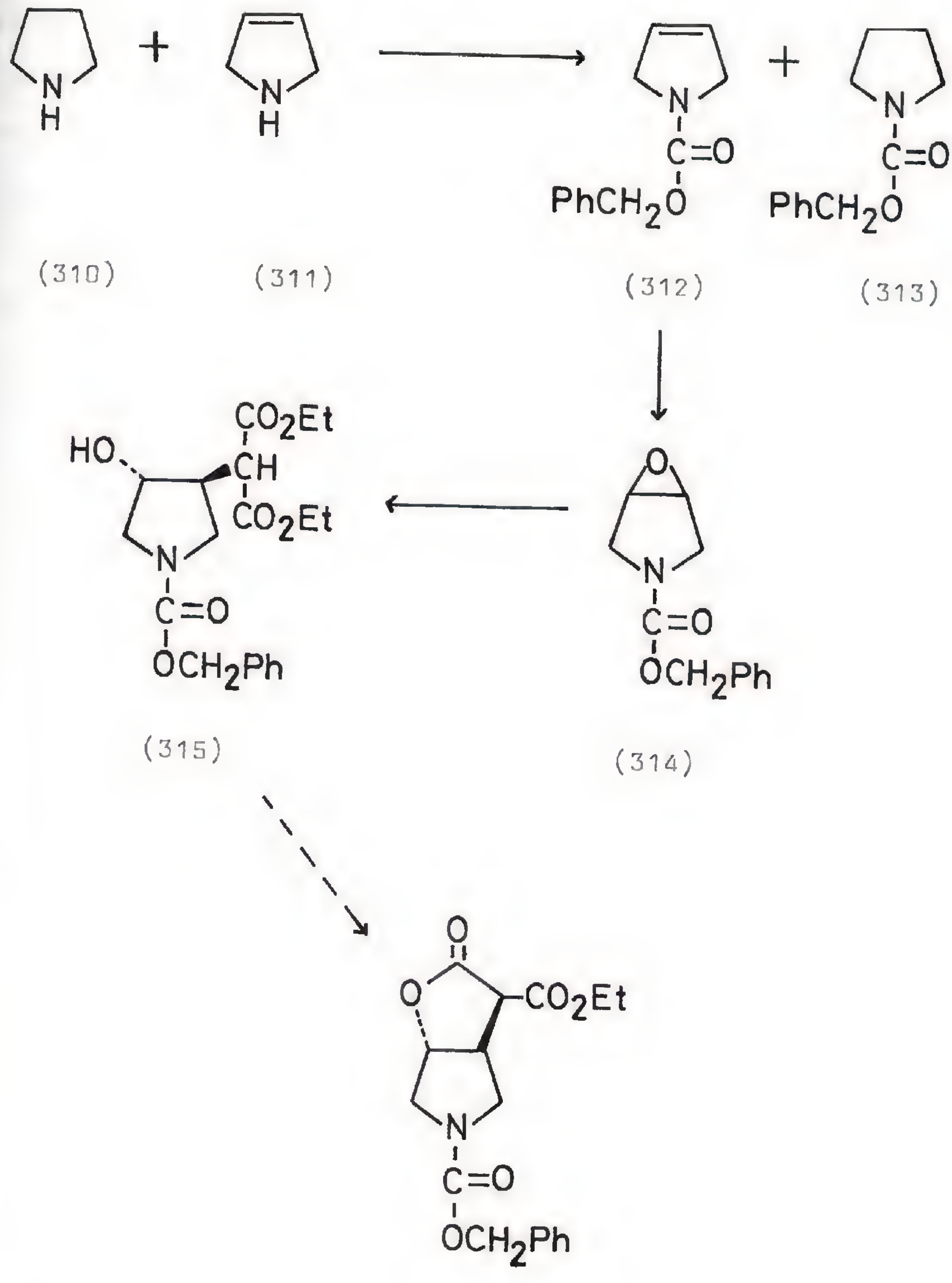
(2) resembling β-aminomethyl-γ-butyrolactone: both (B) and (C) belong to this class;

(3) resembling α-aminomethyl-γ-butyrolactone: only (D) belongs to this category.

(4.1) Pyrrolidine analogues

The reactions involved in this synthesis are charted in Scheme 64, which will eventually lead to an (A)- or (B)-structured compound. It is worthwhile to point out that the preparations of (312) and (314) have already been claimed[283] [also see later (p. 162)].

3-Pyrroline [(311), supplied by Aldrich Chemical Company in 75% purity and being contaminated by 25% of pyrrolidine (310)] was used in the synthesis. Thus the protection of the amino function by benzyloxycarbonylation gave, in quantitative yield, a mixture of the saturated compound (313) and the alkene (312) in a ratio of 25:75, as indicated by PMR and CMR spectra. However, these two compounds could not be separated by chromatographic methods. Fortunately, the epoxide (314), prepared by epoxidation of the allylic amine (312), using *meta*-chloroperbenzoic acid, could be isolated in almost pure form by column



(310) (311) (312) (313)

(315) (314)

(316)

Scheme 64

chromatography. The yield of this oxidation product from the commercially available 3-pyrroline was 42%. The epoxide (314), shows signals (^{1}H NMR) at δ3.38 (1H) and 3.43 (1H) assigned to two oxirane protons, both distorted doublets ($\underline{J}$ = 2 Hz), and signals at δ3.84 (2H) and 3.94 (2H), both as doublets ($\underline{J}$ = 9 Hz) assigned to the non-equivalent pyrrolidine methylene protons (Spectrum P-31). The pyrrolidine ring carbon atoms give signals in the ^{13}C-NMR spectrum at δ 47.26, 47.52, 54.94 and 55.53. Even though the molecule is apparently symmetrical, we believe that the shielding and deshielding effect of the carbonyl function of the benzyloxycarbonyl-protecting group can affect the chemical shifts of half of the pyrrolidine ring. Therefore, in the CMR measurements, 2 signals (one at lower field) for each pair of hetero-linked carbon isotopes (i.e., at δ 47.26, 47.52, 54.94, 55.53) could be located (Spectrum C-31).

By coincidence, the compounds [(312) and (314)] (see p. 161) have also been made in a conformational study of 3,4-epiminopyrrolidines.[283] However, no NMR details have been disclosed in this paper.

Epoxide ring opening with diethyl sodiomalonate in the usual manner gave the alcohol (315). However, unlike the open-chain oxiranes, which provides cyclization products upon acid washings, no lactone was formed [e.g., (316)]. Although the yield of the hydroxy ester (315) was poor (22%), it did afford satisfactory physical

data to support its structure. The IR spectrum of (315) shows OH (3400 cm^{-1}), carbonyl ester (1710 cm^{-1}), and urethane (1680 cm^{-1}) signals, but no γ-lactone carbonyl absorption. The ^1H NMR spectrum shows two almost overlapping sets of ethoxy signals, the newly created carbon-junction proton appears at $\delta 2.72$ and the N-linked pyrrolidine protons resonate between δ 3.18 and 3.5 (Spectrum P-32). These findings are further confirmed by ^{13}C-NMR spectroscopy (Spectrum C-32) and microanalysis.

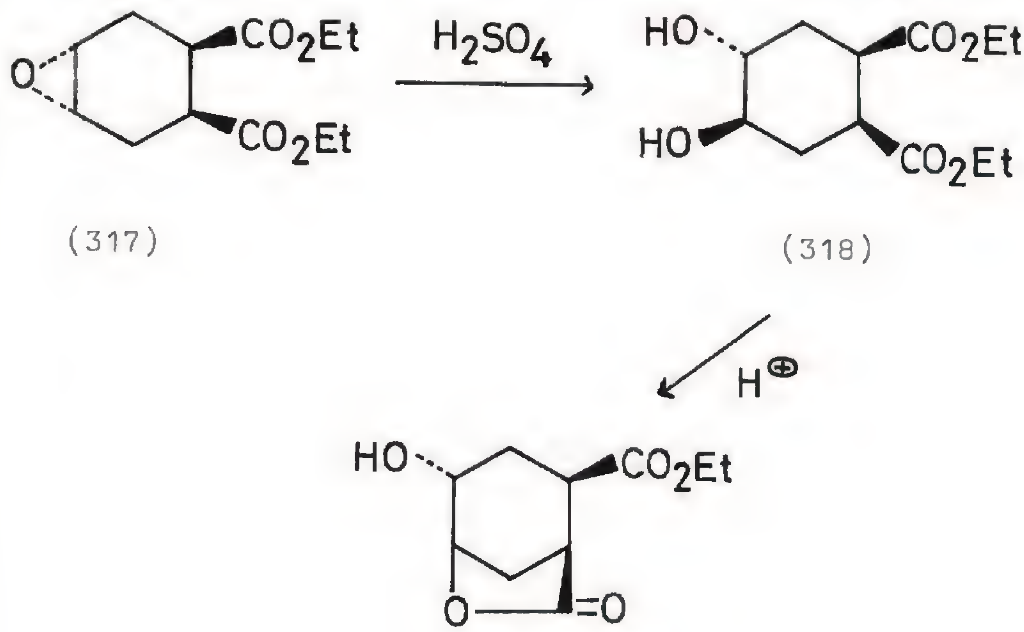
Nucleophilic substitution of epoxides is usually an S_N2 process.[284] Thus a trans-compound is obtained. In the present case, the hydroxy ester [e.g., (315)] is thus in a trans configuration. However, due to steric effects, the cyclization of a cis-hydroxy-ester to form a lactone is always easier than that of a trans-isomer. For example, in the acid hydrolysis of the trans-4,5-dihydroxycyclohexane-cis-1,2-dicarboxylate [(318), p.165] (effectively an internal cyclization) derived from the corresponding epoxide (317) gives only one lactone (319) (Scheme 65), where the more favourable cis-hydroxy-ester lactonized.[285] However, the preparations of some trans-bicyclic-γ-lactones [e.g., (320)][255] and some cytotoxic sesquiterpene lactones[286] (e.g., vernolepin) have also been reported. Ring opening of (321) (see p. 166) with a sterically hindered carbanion derived from diethyl methylmalonate (322) affords the hydroxy ether (323).[287] The authors explain the formation of the ether (323) by the fact that the peri-methyl group in (321) hinders the

approach of the more nucleophilic carbanion to the benzylic carbon atom of (321), so that ethanol (solvent) or ethoxide ion, though a weaker nucleophile than the carbanion, effectively competes in the ring-opening process to furnish the product[287] (323) (Scheme 66) (see p.166).

In the hope that the trans-hydroxyester (315) (p.161) would cyclize under more forcing conditions to afford the corresponding lactone (316), neat trifluoroacetic acid was used. However, only removal of the N-benzyloxycarbonyl group occurred. Even after extensive purification, only a hydroxy ester was obtained, which was tentatively assigned as (324) (p.166), based on its spectroscopic data (IR and PMR). In order to confirm the structure of (324), perbenzoylation was carried out, but failed. Furthermore, treatment of (324) with 6N hydrochloric acid (refluxing) did not give the required monobasic acid. Only decomposition products were obtained. Thus the above evidence ruled out the structural assignment of this compound. No further work was done on this series of synthesis.

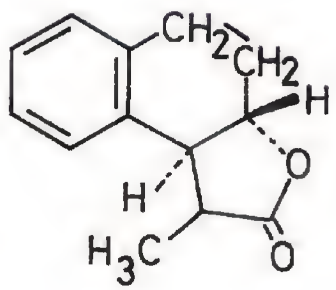
(4.2) Piperidine analogues

All four structural isomers (A-D) can be made and were attempted.

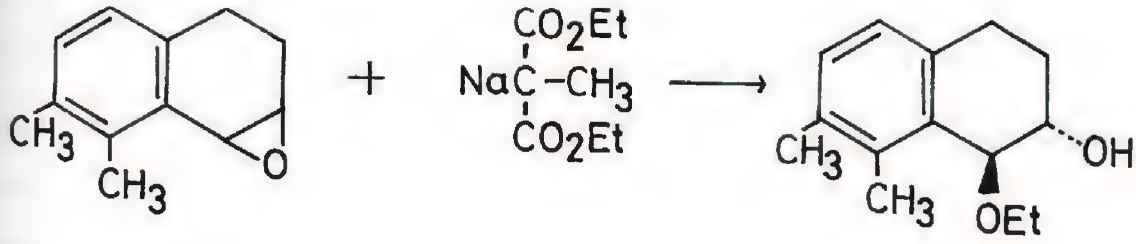


(317) (318) (319)

Scheme 65

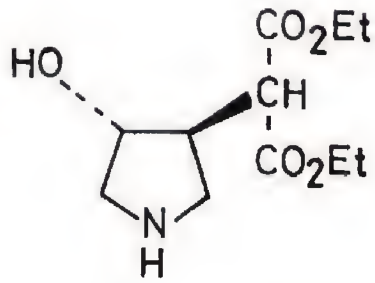


(320)



(321) (322) (323)

Scheme 66



(324)

(4.2.1) Synthesis from tetrahydropyridine (325)

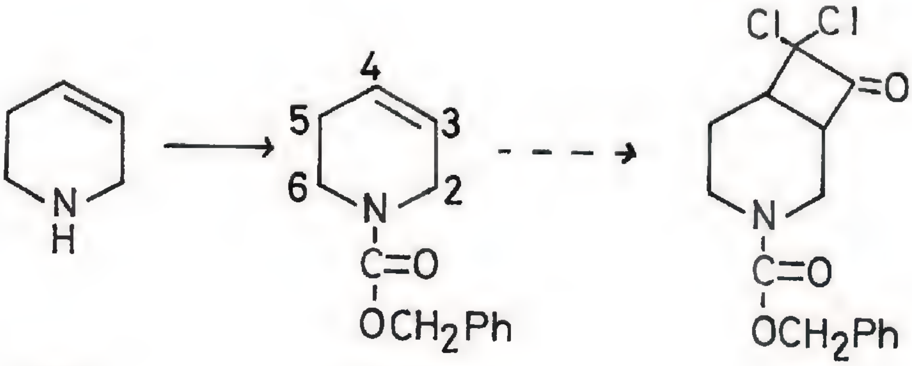
Two routes were tried for the preparation of the needed γ-lactones [e.g.,(328) and (329)]. For both reactions, the common intermediate, the N-protected tetrahydropyridine (326) was required. On scanning the literature, it was discovered that this compound (326) had appeared in patents.[288] However, no details have been disclosed. Similar compounds with ethoxycarbonyl and methanesulphonyl groups at the 1-position have also

been reported.[289] Thus the benzyloxycarbonyl-protecting group was introduced to (325) by the standard procedure in 69% yield. The ^{1}H-NMR spectrum of the compound (326) shows a triplet at δ3.56 ($\underline{J}$ = 6 Hz) (2H-6) and an apparent quintet at δ3.96 ($\underline{J}$ = 3 Hz) (2H-2) [see (326) for numbering] respectively, and all the other protons appear as multiplets (Spectrum P-33). The C-13 NMR spectrum shows expected signal for all the aza-heterocyclic ring carbon atoms (Spectrum C-33).

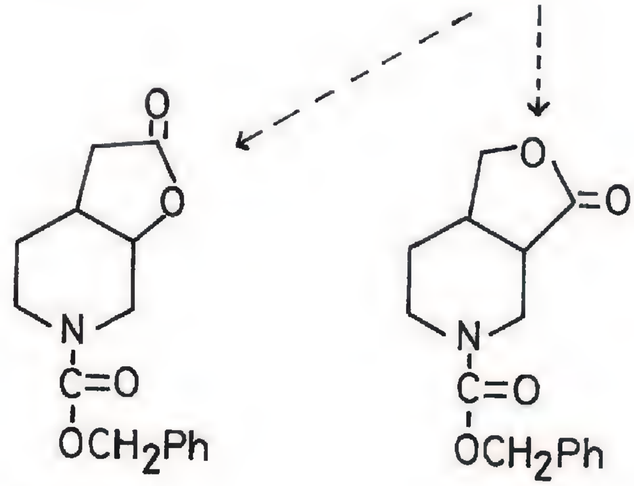
(4.2.1.1)<u>Via a [2+2] cycloaddition reaction</u>

[2+2] Cycloaddition of dichloroketene to alkene has been widely utilized in synthetic chemistry.[290] Originally, we had planned to employ this method to produce the dichlorobutanone (327). By analogy to reported compounds, derivatives such as (327) would be expected to be formed regiospecifically.[291] Dehalogenation should provide the required butanone, which on Baeyer-Villiger oxidation[143,292] should afford the γ-lactone [(328) or (329)]. The literature procedure[290b] was carried out but without success. Attempts to improve the reaction included: increasing the amount of input dichloroketene (<u>i.e.</u>, dichloroacetyl chloride /triethylamine) and varying the temperature and time. There was still no reaction. Some extra low field signals were observed in the NMR spectrum of the crude mixture, perhaps due to the polymeric material formed as a result of di- or trimerization of the unreacted dichloroketene. It is of interest to know that some less

(A)

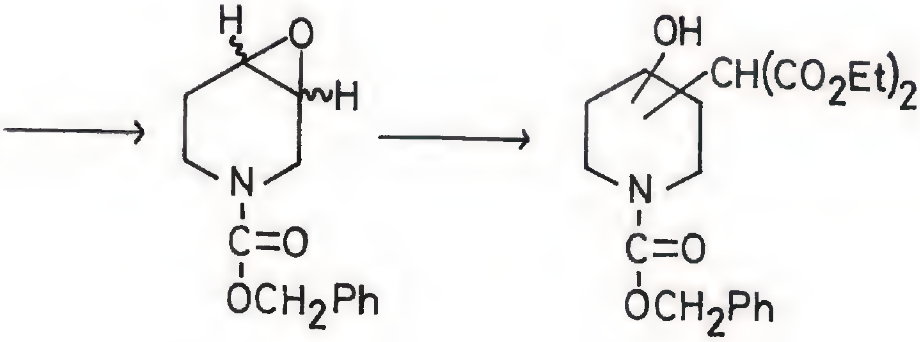


(325) (326) (327)



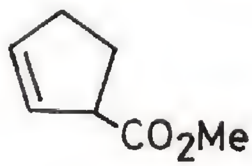
(328) (329)

(B) (326)



(330) (331)

Scheme 67: (A) and (B)



(332)

electron-rich molecules, which similarly possess an electron withdrawing substituent, [e.g., (332)] also fail to produce adducts.[293]

(4.2.1.2) Through the epoxide (330)

The required epoxide (330) was prepared by the usual procedure from (326) in 55% yield. The synthesis of the corresponding N-ethoxycarbonyl and N-methanesulphonyl compounds has already been disclosed.[289] Two compounds (presumably isomeric oxiranes) running with close Rf values were observed by TLC analysis. However, clean separation of them by column chromatography could not be achieved. Thus these two isomers were used together in the next stage of the transformation (Scheme 67) (see p.168). The ^{1}H-NMR spectrum of this mixture of isomers (330) showed unresolved multiplets for all the piperidine ring protons, nevertheless a satisfactory integration could be obtained for these signals. In the ^{13}C-NMR spectrum a 2:1 mixture of isomers was strongly indicated, from the relative intensity of the duplicate resonances.

Ring opening of the oxirane (330) with diethyl sodiomalonate gave the hydroxy ester as a crude mixture in very low yield. Attempts to purify the product by cyclization to a lactone under more stringent conditions or to isolate it as the mono O-benzoate failed, inconsistent results being obtained.

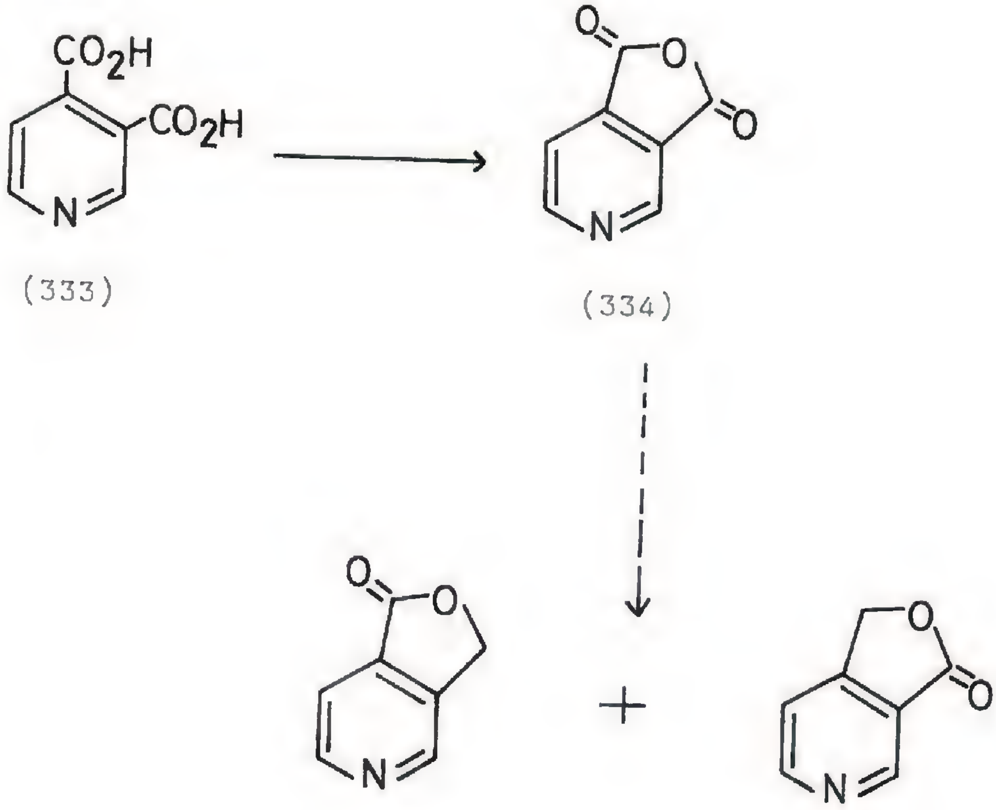
Unfortunately these results in the pyrrolidine and piperidine series suggested that this approach to GABA

analogues was unlikely to be useful. This led us to abandon this approach altogether.

(4.2.2) Synthesis starting from pyridine-3,4-dicarboxylic acid

The use of the more flexible protected piperidine derivatives had given us more problems than we had anticipated. We therefore decided to attempt to prepare the lactone attached to an aromatic ring, with the hope of reducing the aromatic ring in a final step. The chemistry of pyridine is well-studied.[294] There is also precedent for the synthesis of pyridine analogues of phthalide.[295] If required, some other useful functional groups [e.g., nitro, sulpho and alky (or precursor)] can also be introduced during certain stages of the transformation. In fact, this constitutes an approach which is very similar to those used in the monocyclic γ-lactone series.

In the first instance, we thought the reduction of an acid anhydride[128,144] [e.g., (334)] might be suitable, which should give us the two isomeric lactones [(335) and (336)] (Scheme 68) very directly. Thus the anhydride (334) was prepared by the reported procedure.[296] However, reduction using sodium borohydride, which has been commonly employed in the reduction of anhydrides to lactones, failed. There might have been a minute amount (less than 5%) of the product formed, as detected by NMR spectroscopy. We therefore reverted back to the literature method.[295] The required diethyl diester (337) could be prepared by either refluxing of the acid anhydride



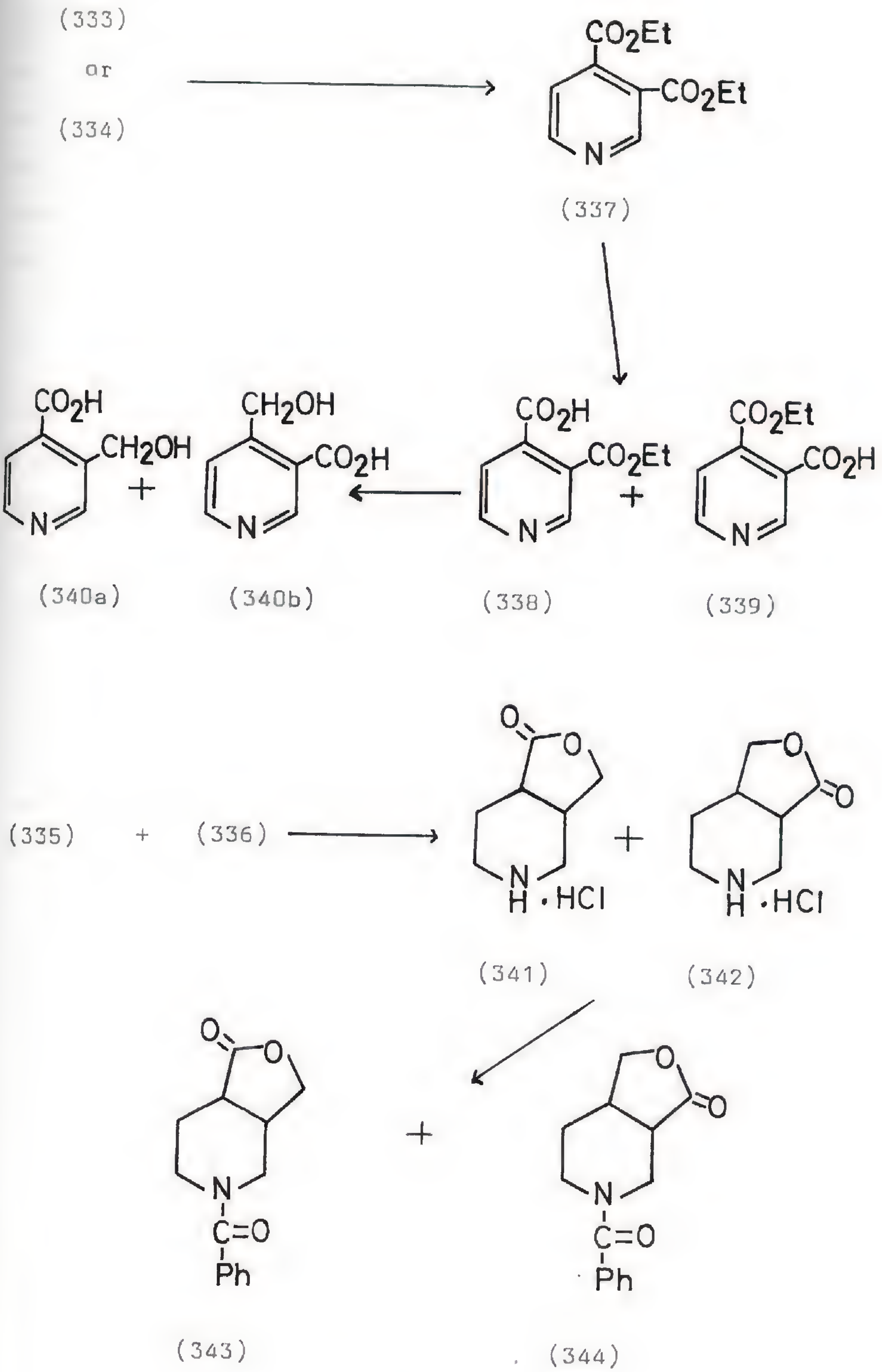
(333) (334)

(335) (336)

Scheme 68

(334) or the diacid (334) in ethanol in the presence of concentrated sulphuric acid[297] in quantitative yield. In the ^{1}H-NMR spectrum, 2 sets of ethyl proton signals were recorded: C-5 and C-6 protons resonated at δ7.51 and 8.85, respectively, as doublets and C-1 proton at δ 9.08 as singlet (Spectrum P-34). The ^{13}C-NMR spectrum also gave the expected resonances for the carbon isotopes (Spectrum C-34).

Base hydrolysis of the diester (337) using just one equivalent of sodium hydroxide gave the 3-monoester

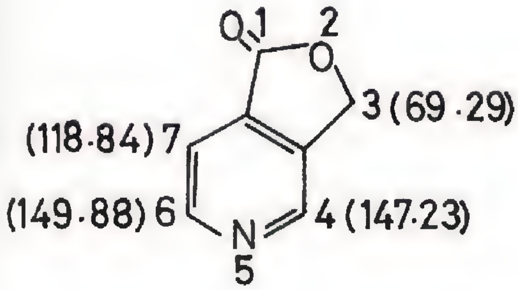

(333)
or
(334)
CO_2Et
CO_2Et
N
(337)
CO_2H
CH_2OH
+
N
CH_2OH
CO_2H
N
CO_2H
CO_2Et
+
N
CO_2Et
CO_2H
N
(340a)
(340b)
(338)
(339)
(335)
+
(336)
O
O
N
H · HCl
+
O
O
N
H · HCl
(341)
(342)
O
O
N
C=O
Ph
+
O
O
N
C=O
Ph
(343)
(344)

Scheme 69

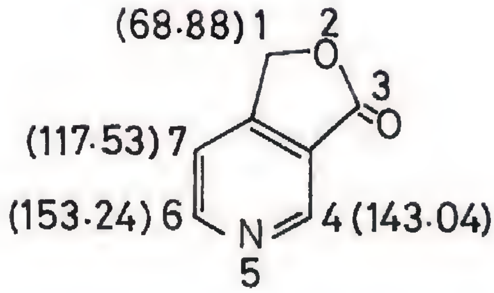
(338) in low yield (20%) after neutralization, which was obtained as crystalline solid. The filtrate was thus a mixture of the two isomers [(338) and (339)] which constituted an overall yield of 60%. The NMR measurements of the more pure pyridine-4-carboxylic acid (338) were identical to those reported by Joule[295] (Spectrum P-35 and C-35).

Attempts to reduce the ester [e.g., (338)] with sodium borohydride or old stock of lithium aluminium hydride failed. However, by the time a fresh supply of lithium aluminium hydride arrived, all the pure (338) had been used up. Thus the reduction was conducted as reported[295] with the mixture of monoesters [(338) and (339)], which gave isomeric alcohols [(340a) and(340b)] in 80% yield. These were spectroscopically consistnent with their assumed structures. Without further purification, the hydroxy acids were converted to the lactones[(335) and (336)] using dicyclohexylcarbodiimide as the condensing agent in aqueous tetrahydrofuran.[295] This was a poor yielding reaction (10%). It was possible to differentiate the two UV-active products by TLC analysis; however, a very polar solvent system [a mixture of ethanol and ethyl acetate (1:2)] was required. In practice, no separation could be achieved using ordinary gravity silica gel column chromatography. The chromatographic behaviour of these lactones [(335) and (336)] has not been published before. Thus, for the ease of discussion, the faster running spot was assumed to be the lactone (335). However, the assign-

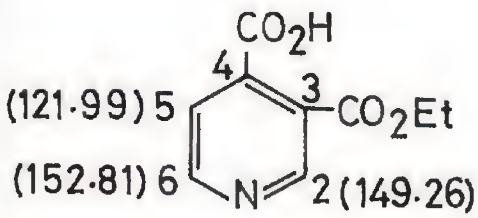
ment might be otherwise (and also see later for the structural assignment of the saturated derivatives). According to NMR spectral data, these isomers were obtained in a ratio of almost 1:1. The C-13 NMR measurements of some carbon atoms are displayed in the structures, for the sake of comparison, which are identical to the reported values.[295]



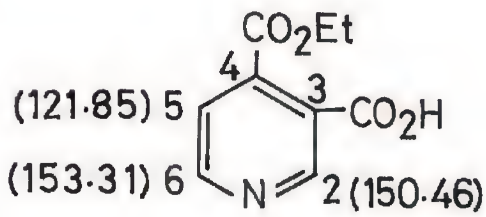
(335)



(336)



(338)



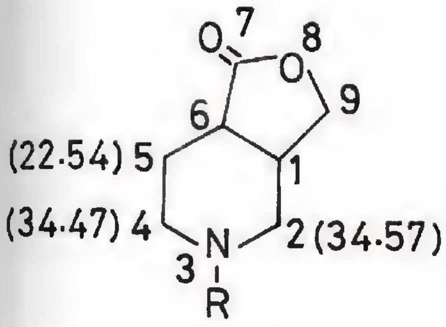
(339) *

N.B. δ values are in brackets (also see Experimental Section).

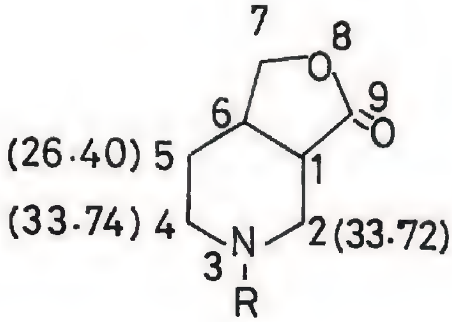
* quoted from literature.[295]

Catalytic hydrogenation of pyridine has been studied,[298] and the specific use of 10% palladium-on-charcoal as catalyst has been reported.[299] However, it failed on our system. Finally, the reduction was effected with Adams' platinum catalyst in the usual fashion to give the ammonium chlorides [(341) and (342)] in excellent yield. Since in catalytic reduction, the incorporation of hydrogen is through one face of the molecule as the other is bound to the catalyst, usually one stereoisomer (the <u>cis</u> compound) is formed. Only two isomers were obtained after <u>N</u>-benzoylation assigned structures [(343) and (344)], which could be readily separated. The isomer eluted off first during column chromatography was assigned (343) (see later for confirmation of the structures).

Unsurprisingly, the ^{1}H-NMR spectra of the isomers [(343) and (344)] proved to be complex,[300] but were apparently consistent with the general structure proposed for these compounds. ^{13}C-NMR spectral analysis of piperidines has been studied recently.[301,302] In the ^{13}C spectra, the most noticeable difference in the signals of (343) and (344) are due to those of C-2, C-4 and C-5 (for numbering of the structures see the next page). For the "phthalides" [(335) and (336)], no correlation could be drawn for the anisotropic effect of the carbonyl group on C-4 and C-7 (see p.174 for numbering). Perhaps, in these examples, the chemical shifts of the aromatic ring carbons are mainly determined by the diamagnetic shielding effect (involving electrons on the nucleus).[155] Unlike the pyridine case



(343)



(344)

N.B. R = $\mathop{\mathrm{C}}\limits_{\substack{\Vert\\ \mathrm{O}}}\mathrm{Ph}$

above, in the saturated derivatives, as we can see from the structures, the anisotropy of the carbonyl group is marked: in (343) C-5 is shielded (resonates at δ 22.54) while in (344) C-5 is deshielded (δ 26.40). For the assignment of the two CH_2N carbon isotopes, in (343) C-2 (δ34.57) and C-4 (δ 34.47), while those of (344) C-2 (δ 33.72) and C-4 (δ 33.74), similarly due to deshielding and shielding effect,[154] respectively (see also the assignment of the α,β-unsaturated ester (114) (p.57). Furthermore, IR spectra, microanalyses and mass spectra of these compounds also support the structures of (343) and (344).

(5) Synthesis of amino sugar lactones as GABA analogues

For a variation of the substituents on the lactone rings and also the side-chains, the readily available aldonic acids and glycosides are useful starters for chemical manipulation towards the goal of preparing structural analogues of GABA. Carbohydrate derivatives such as alditols (e.g., mannitol), lactonic acids (e.g., ascorbic acid[303]) and antibacterial glycosides (e.g., the amino-sugars, gentamycin and streptomycin[304]) are medicinally useful compounds.[305]

Utilization of sugar molecules as synthetic intermediates for natural and unnatural products has been widely studies [246] (for example, in the recent review on the formation of convenient chiral intermediates from carbohydrates and their use in synthesis by Inch[246b]). Carbohydrates provide valuable chiral substrates for the synthesis of enantiomerically pure chiral products, particularly natural products.[145a,b]

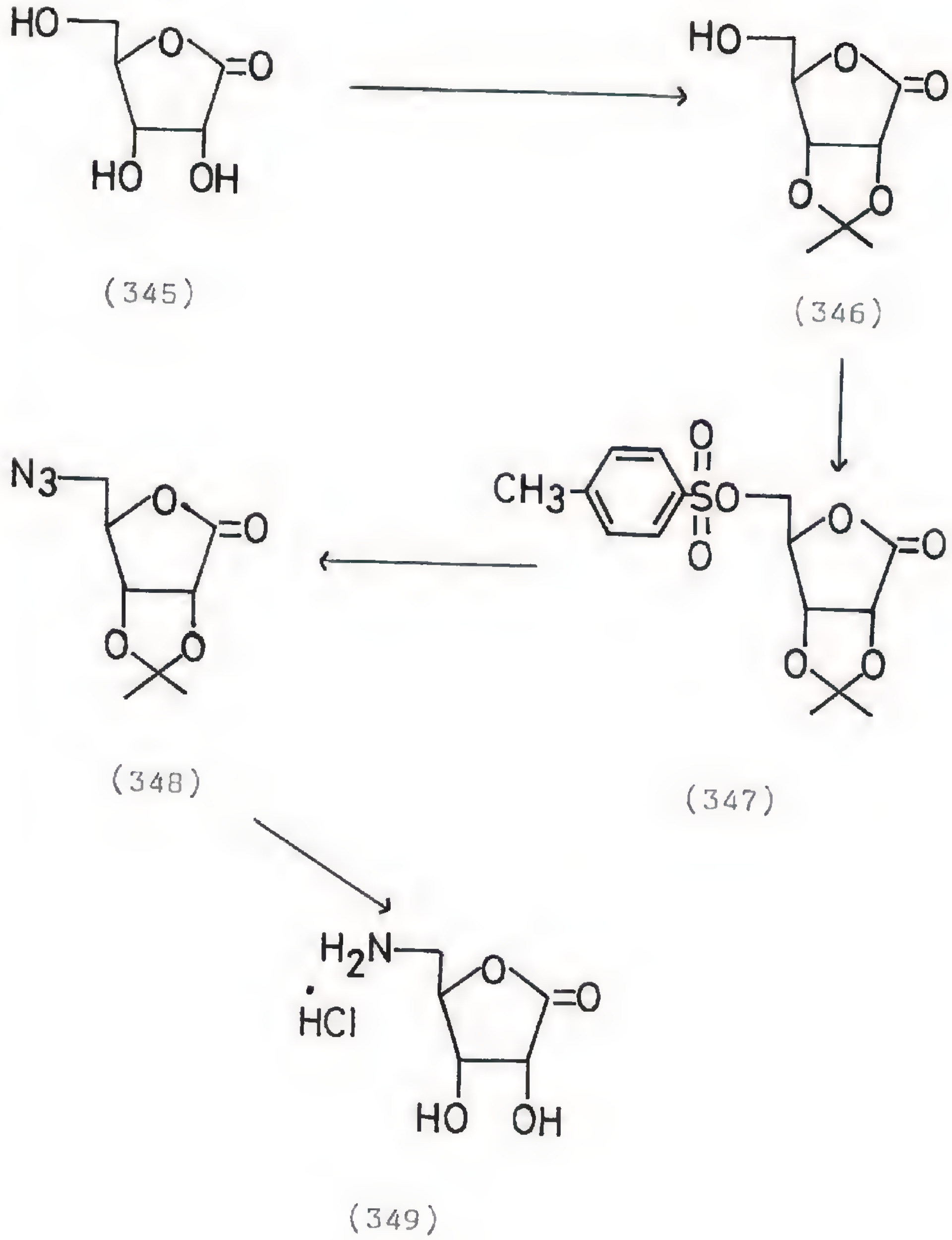
In this dissertation, an effort had been made to prepare some lactonic carbohydrate derivatives that possess structural features of GABA, either in a straight bicuculline sense (e.g., 5-amino-5-deoxyaldono-1,4-lactones) or with a direct GABA skeleton (as in 3-substituted branched-chain sugars). The rationale behind these constructions is the same as those in the γ- and β-aminomethyl-γ-lactones (Section 1 and 2).

(5.1) 5-Amino-5-deoxyribono-1,4-lactone (349)

(A) Synthesis

The sequence employed for the synthesis was based on that reported in the literature by Hanessian[306] (with some modifications), outlined in Scheme 70. Initial attempts to selectively sulphonate the terminal primary hydroxyl group (by controlled use of reagent at low temperature) were unsuccessful. A similar failure has been reported in the literature.[307] The 2,3-O-isopropylidene derivative (346) was therefore prepared. Reaction of D-ribono-γ-lactone (345) with 2,2-dimethoxypropane in the presence of a catalytic amount of tosic acid led to the acetal (346) which was obtained as an off-white solid.

Tosylation of the monohydroxy compound (346) according to the reported procedure[308] gave an 84% yield of the solid tosylate (347). The displacement of the primary sulphonate ester group in such aldono-γ-lactones should occur as readily as in analoguous alicyclic and aromatic compounds containing sulphonyloxymethyl substituents, so that azide displacement was not expected to present any problems [for similar azide displacement reactions see (e.g., in the β-aminomethyl series, Section 1.2.1.6, and in the γ-aminomethyl series, Sections 2.2.1.3 and 2.2.2)]. However, azidolysis using aqueous acetone as solvent gave only decomposition products. We therefore tried a previously published procedure,[306] (involving heating in DMF and, after reaction, evaporating the solvent in the presence of butyl alcohol and finally extracting the residue with ether). However, no product could be found in the organic layer. Most of the product



Scheme 70

still appeared in the aqueous layer (TLC and IR of the residue after evaporation of water). The work-up procedure was therefore modified, concentrating the solution by solvent evaporation under reduced pressure, purifying the residue by column chromatography to afford the azide (348) in 21% yield, which was still contaminated with a

small amount of DMF and tosic acid, as detected by NMR spectroscopy. A recent paper reports the observation that sulphonate esters which have β-oxygen substituents present are resistant to nucleophilic attack.[309] The synthesis of azide (348) has also been achieved *via* oxidation of 5-azido-5-deoxy-2,3-isopropylidene-D-ribose,[310] and the corresponding 2,3-benzylidene compound was similarly prepared.[306] The 2,3-cyclohexylidene derivative has also been reported.[307b]

Catalytic hydrogenation of the azide (348) in the presence of aqueous hydrochloric acid gave the hydrochloride salt (349) as a brown hygroscopic solid in high yield. The salt (349) was previously described to be a high melting solid (186°). However, in our hands it proved to be air sensitive (like most lactonic ammonium salts prepared in the present work). It was possibly because of the presence of DMF as a contaminant.

(B) Characterization

The published synthesis [306] did not include ^{1}H- or ^{13}C-NMR spectral data. A more recent publication on the use of ribonic acid γ-lactone (345)[311] does furnish data on some compounds analoguous to those we have prepared, facilitating assignment of signals.

The ^{1}H-NMR spectra of the ribonic acid derivatives show that, for the ring protons, H-2 always appears as a doublet, (J = 6 or 8 Hz), H-3 as a doublet of doublets (J = 3 and 8 Hz)

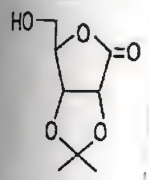
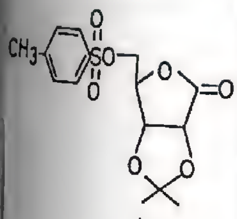
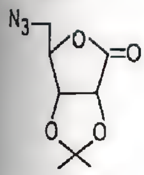
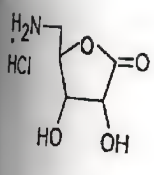
or just a doublet ($\underline{J}$ = 6 Hz) and H-4 as a triplet ($\underline{J}$ = 3 Hz). The exoxyxlic methylene protons resonate either as distorted AB quartets [(346) and (347)] or as doublet of AB quartets [(348) and (349)]. In the hydroxy compound (346), the H-5 signals appear at δ4.25 as a doublet of doublets ($\underline{J}$ = 2 and 13 Hz) and at δ 4.35 as a doublet ($\underline{J}$ = 13 Hz) (Spectrum P-36). A similar pattern is observed for the tosylate (347) (Spectrum P-37). The resonances of the methylene protons of the azide (348) and the ammonium salt (349) (Spectrum P-38) are at δ 3.70 and 3.42 respectively, both as doublet of AB quartets (J = 2 and 14 Hz).

In the ^{13}C spectra, the most distinctive changes in the chemical shifts occur for C-5, due to the effect of the attached substituents. The ^{13}C spectral data of this series of compounds are listed in Table 9 and in Spectra Section C-36, C-37 and C-38 for compounds (346), (347) and (349) respectively.

(5.2) Branched-chain sugar derivatives as GABA analogues

Branched-chain sugars are unusual in not having a linear carbon backbone.[312] Such sugars are primarily components of antibiotics produced by microorganisms, such as streptose, but several are plant products, e.g., apiose[313] and hamamelose. A review covering the synthetic chemistry of branched-chain mono- and disaccharides has been published recently.[314]

Table 9 : ^{13}C chemical shifts of some 5-substituted D-ribono-1,4-lactones

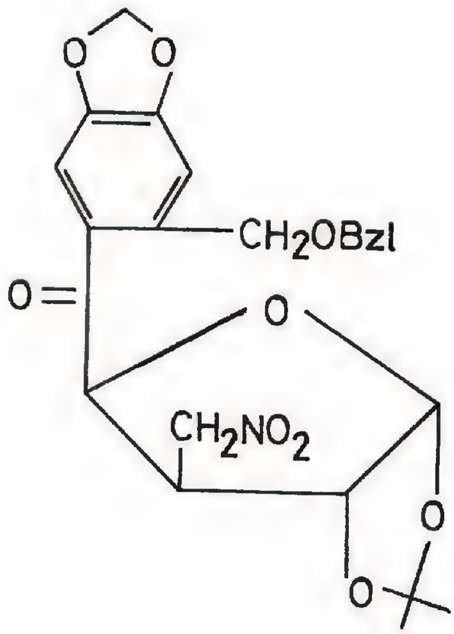
Compounds	Solvent (frequent)	C-1	C-2	C-3	C-4	C-5	Other carbons
 (346)	pyridine-d^5 (15 MHz)	171.35	72.20	68.22	75.45	66.08	22.59, 24.54 and 108.33
 (347)	$CDCl_3$ + pyridine-d^5 (15 MHz)	177.40	74.54	73.30	75.06	67.77	21.48, 24.21, 25.91, 111.13, 128.44, 130.01, 133.91, and 145.57
 (348)	$CDCl_3$ (15 MHz)	174.08	78.25	75.26	80.40	52.53	25.52, 26.69 and 113.86
 (349)	D_2O + TSP (50 MHz)	177.74	74.31	72.27	76.83	45.17	

(5.2.1) Via 1,4-addition to α,β-unsaturated compounds

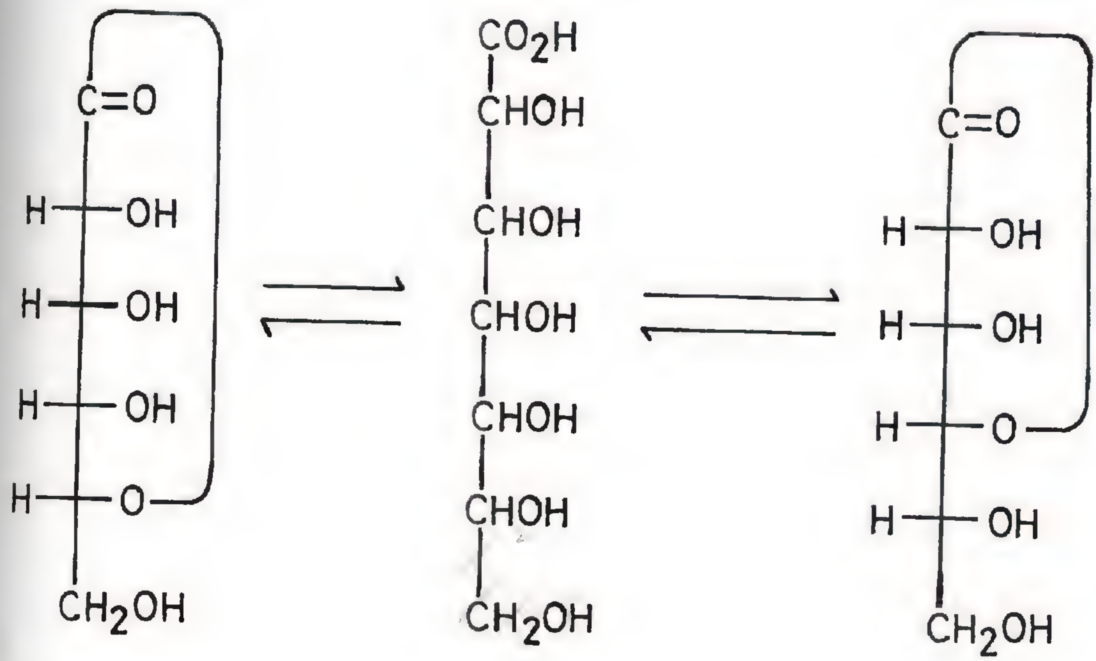
As in the β-aminomethyl series of monocyclic -lactones, addition of a masked amino-carbanion (especially that of nitromethane) to α,β-unsaturated esters give latent aminomethyl compounds could provide a useful approach. Furthermore, an analogy is provided by the Michael addition of a nitromethyl group to an α,β-unsaturated glycosulose giving a branched-chain sugar[315] [e.g., (350)]. The discussion is limited to the attempts using α,β-unsaturated sugar lactones as starting materials.

(5.2.2) Starting from D-gluconolactone

We first tried to isomerize D-glucono-1,5-lactone to the 1→4-isomer by the method of Isbell and Frush[316] (351)→(353) Scheme 71. However, in our hands, the hygroscopic γ-lactone (353) proved to be difficult to isolate in pure form. Thus an alternative process was sought. It was hoped that in the presence of acid, equilibration of the γ- and δ-lactones would allow the efficient formation of the 5,6-O-acetal of the γ-lactone (355). Thus the reaction of D-gluconolactone (354) with 2,2-dimethoxypropane in the presence of p-toluenesulphonic acid as catalyst by refluxing for ca. 3 hours or by stirring at room temperature for 2 days gave a protected trans-dihydroxy compound [(355) or (356)]. The infrared spectrum of this compound indicated that it still possessed hydroxyl groups, whereas the ^{1}H-NMR spectrum ascertained the incorporation of isopropylidene moiety. However, the

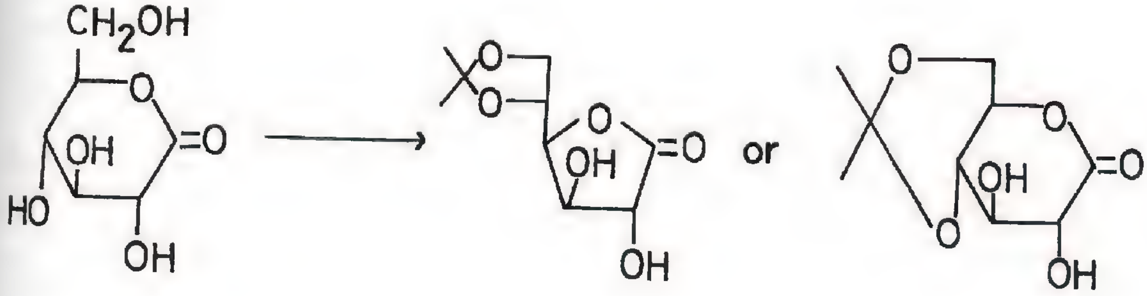


(350)

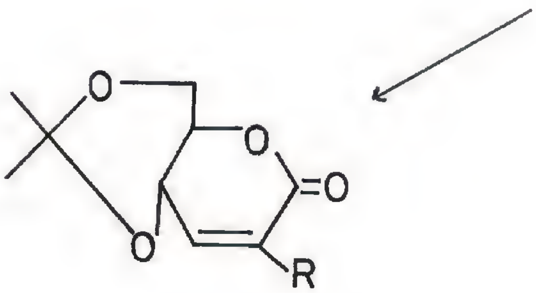


(351) (352) (353)

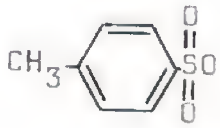
Scheme 71



(354) (355) (356)



(357) R = $CH_3\underset{\underset{O}{\|}}{C}O$

(358) R = 

(359) (360)

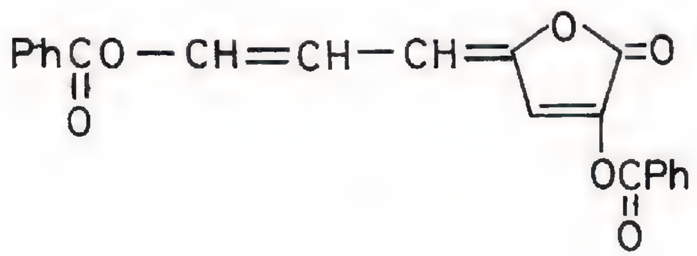
(361) (362)

cyclic ether [(355) or (356)] was contaminated with some residual 2,2-dimethoxypropane. Initially, we had assumed the product as the γ-lactone (355). However, recently a patent[317] was published to claim for the preparation of a 4-6-benzylidene-δ-lactone from D-gluconolactone, using similar acid-catalyzed conditions for the benzylidenation. Therefore it was possible that (356) was the compound we had made.

Acetylation or sulphonation of the diol (356) gave the corresponding β-eliminated compounds,[318] the monoacetate (357) and the monotosylate (358). Attempts to reduce the double-bond by catalytic hydrogenation using 10% palladium-on-charcoal as catalyst at ordinary temperature and pressure resulted in no reaction. However, the hydrogenation of the acetylated γ-lactone (359) to the 3-deoxy lactone (360) has been reported[319] under the conditions we used. This same paper also reported that the hydrogenation of the isomeric δ-lactone (361) to (362) required high pressure (100 atm). This further suggested that the parent compound (356) was a δ-lactone.

The ^{1}H-NMR spectrum of the acetate (357) shows a distinctive vinylic proton (C-3) at δ5.30 as a doublet ($\underline{J}$ = 2 Hz) and C-4 proton at δ4.46 as a doublet of doublets [$\underline{J}_{(3,4)}$ = 2 Hz and $\underline{J}_{(4,5)}$ = 8 Hz]. A similar pattern of coupling is observed in the spectrum of the monotosylate (358): C-3 proton at δ 5.18 [d, $\underline{J}_{(3,4)}$ = 2 Hz] and C-4 proton at δ4.5 [dd, $\underline{J}(3,4)$ = 2 Hz and $\underline{J}_{(4,5)}$ = 8 Hz]

(Spectrum P-39). In the ^{13}C-NMR spectra, the most distinctive change from the diol (356) to the α,β-unsaturated compounds [(357) and (358)] is the disappearance of C-2 and C-3 signals at δ 80.97 and 76.60 respectively, which are replaced by unsaturated carbon signals at δ 110.46 [for (357), C-3] and 111.04 [for (358), C-3]. It is of interest to notice that for some reported α,β-unsaturated aldonolactones, e.g., 3-benzoyloxy-5-(3-benzoyl-oxyallylidene)-(5H)-furan-3-one (363), the C-13 NMR spectra give signals at ca. δ 138 for C-2.[320] However, we did not



(363)

observe any signals in this region for our compounds. The ^{13}C spectrum of compound (358) can be found in Spectra Section (C-39).

Attempts to add nitromethane to either (357) or (358) by various methods failed. Methylation of the diol (356) and subsequent elimination of methanol by 1,5-diazabicyclo[4.3.0]non-5-ene was also not successful. Other failed reactions include: (1) selective preparation of monoacetal (356) using 2-methoxypropene,[321] (2) Corey-

Winter reaction[322] on (356) and also the triphenylphosphine/ imidazole/iodine procedure[323] on (356) and (3) monotritylation of D-gluconolactone.[324]

(6) Biological results

The racemic sulphonate salt (120b) and the enantiomerically pure hydrochloride salt (232) were tested as GABA analogues by Dr. N. Bowery. Department of Pharmacology, St. Thomas' Hospital Medical School, in 1983, but were found to be inactive. However, a potent GABA agonist activity for (232) was indicated in the preliminary assays on spinal cord (presumably not on the same tissues as in the above experiments) by Dr. A. Nistin, Department of Pharmacology, St. Bartholomews' Hospital Medical School.

Conclusion

Some neuroactive aminomethyl-γ-lactones were successfully prepared as GABA analogues. The β-aminomethyl-γ-butyrolactone salts [(120a) and (120b)] were obtained by the catalytic hydrogenation of the azide (119), the nitro compound (182) and the azido-2-butenolide (202). To synthesize the enantiomerically pure and racemic γ-aminomethyl-γ-butyrolactones [(232) and (252), respectively], the azides[(231) and (251)] were similarly hydrogenated. The racemate (252) was also formed by the reaction of the epoxide (272) with diethyl sodiomalonate. A literature procedure was used to prepare α-dimethylaminomethyl—γ-butyrolactone (299a). The piperidinium salt (246b) was obtained from the tosylate (230) by displacement with piperidine and followed by ion-exchange. However, the parent compound (308a) could not be made.

After several attempts in the synthesis of some of the aza-heterocyclic lactones [e.g., (316)] from saturated azole and azine derivatives, two isomeric piperidines [(341) and (342)] were produced by the hydrogenation of the known furo[3,4-C]pyridin-1(3H)-and-3(1H)-ones [(335) and (336), respectively] using Adams' platinium catalyst. These primary and secondary amine salts were further characterized as their N-benzoates [(183), (233), (253) and (343)-(344)].

The amino sugar lactone (349) was synthesized by a reported procedure. However, attempts to prepare the branched-chain sugar lactone analogues failed.

EXPERIMENTAL

Apparatus, Chemicals and Methods

Temperature

Ambient or room temperature refers to the range 15-30^{o}C.

Melting points

Melting points were determined with a Reichert apparatus, and are reported in degrees centigrades, uncorrected.

Optical rotations

A polarimeter with a sodium light source, manufactured by Optical Activity Ltd., was used. A 1-ml polarimeter tube was employed for all the measurements. The concentrations and solvents were stated. The temperature of the apparatus was also noted.

Infrared spectra

These measurements were carried out with a Perkin-Elmer Infrared 297 or 597 spectrophotometer. Solids were usually mulled with Nujol before applied onto KBr discs and spectra were then recorded. Gums or oils were measured as smears on KBr discs. Some were also dissolved in tribromomethane, trichloromethane or tetrachloromethane

as *ca*. 1% solutions and then enclosed in 1-cm sodium chloride cells and the spectra were usually run alongside with references. Absorption maxima (υ_{max}) are reported in wave numbers (cm^{-1}).

Nuclear magnetic resonance spectroscopy

(A) Proton magnetic resonance (PMR) spectra

Most of these determinations were performed on a Jeol JNM-FX200 Fourier Transform NMR spectrometer, Jeol JNM-MH-100 or Hitachi Perkin-Elmer R-24B spectrometer but a few were measured on a Varian A-60D spectrometer in the stated solvents. Chemical shifts are quoted in δ values relative to tetramethylsilane(TMS) or 3-(trimethylsilyl) propionic acid sodium salt (TSP) as an internal standard. However, in a few cases, when Fourier transform spectra were run in D_2O, internal standards (*e.g.*, TSP) were not added. The HOD signal (*ca*. δ 5.2) was programmed as the standard and the chemical shifts of the other signals were adjusted according to it. Signals are described as s(singlet), d(doublet), dd(doublet of doublets), t(triplet), q(quartet), qnt(quintet), sxt(sextet), spt(septet): m represents multiplet, and b represents broad, *e.g.*, bs(broad singlet). Spin-spin coupling is indicated by the symbol *J*, with the appropriate subscripts *e.g.*, $J_{(1,2)}$, $J_{(1,4)}$.

(B) Carbon-13 magnetic resonance (CMR) spectra

All the compounds were measured by either a Jeol JNM-FX 200 (operating at 50 MHz) or Jeol JNM-FX 60 (operating at 15 MHz) Fourier Transform spectrometer. All spectra were completely proton decoupled. Chemical shifts are quoted in δ values relative to TMS, TSP, DSS [3-(trimethylsilyl)-1-propanesulphonic acid sodium salt], 1,4-dioxane or 2-propanone as an internal standard.

Chromatography

Reactions were followed by analytical thin layer chromatography (TLC) on Merck F_{254} precoated plates. The following solvent systems were used to develop the thin layer chromatograms:

A = trichloromethane : ethanol (1:1)
B = trichloromethane : ethanol (4:1)
C = trichloromethane : ethanol (93:7)
D = trichloromethane : diethyl ether (1:1)
E = trichloromethane : methanol (9:1)
F = ethanol : ethyl acetate (1:2)
G = ethanol : ethyl acetate (2:1)
H = ethyl acetate
I = ethyl acetate : petroleum ether 40-60^{o} (1:1)
J = ethyl acetate : petroleum ether 40-60^{o} (1:2)
K = ethyl acetate : petroleum ether 40-60^{o} (1:3)
L = ethyl acetate : petroleum ether 40-60^{o} (1:4)
M = ethyl acetate : petroleum ether 40-60^{o} (1:9)
N = ethyl acetate : petroleum ether 40-60^{o} (2:1)

O = ethyl acetate : petroleum ether 40-60^o (4:1)

P = ethyl acetate : 2-propanone : water (10:5:2)

Q = diethyl ether

R = diethyl ether : petroleum ether 40-60^o (1:1)

S = diethyl ether : petroleum ether 40-60^o (2:1)

T = diethyl ether : petroleum ether 40-60^o (3:1)

U = dimethoxyethane : petroleum ether 40-60^o (3:2)

The compositions of solvent mixtures are stated V/V. Products were detected by examination of the chromatograms under UV light, UVSL-58, manufactured by Ultraviolet Products Inc., and by staining with iodine vapour. For carbohydrate derivatives and some oxygenated compounds, in addition to the above-mentioned techniques for visualizing the product spots, the procedure by spraying with a mixture of ethanol and concentrated sulphuric acid (4:1) (V/V) and heating on a hot-plate (_ca_. 150^o) was used.

Preparative column chromatography was carried out on Merck Kieselgel 60 (70-230 mesh) using gravity elution. Ion exchange chromatography was performed on Amberlite IRA 410 (ex-Aldrich), a sulphonated styrene polymer (chloride form)

Gas chromatograms were recorded on the gas chromatographic machine, made by Carlo Erba Strumentazione Co., at the stated temperatures.

Gas Chromatography

(1) 2 m x 6 mm (OD) glass, 5% SE 30 on chromosorb WHP 60-80, inlet pressure (1.0 kg cm^{-2}); as for compounds (109), (112), (114) and (115).

(2) 26 m x 0.5 mm G-SCOT. OV-101, inject temperature 175^{o}, inlet pressure 0.33 kg cm^{-2}; as for compound (231).

Solvents

Benzene, dichloromethane, trichloromethane, anhydrous diethyl ether, dimethoxyethane and N,N-dimethlformamide were dried over molecular sieve (type 4A), tetrahydrofuran was dried and purified by passage through a column of basic alumina and stored over calcium hydride.

Solutions in organic solvents were dried over anhydrous magnesium sulphate or sodium sulphate.

General procedures

(A) Acetalation of sugars

The polyhydroxy compound (64 mmole) was suspended in 2,2-dimethoxypropane (80 ml) and 4-methylbenzenesulphonic acid monohydrate (500 mg) was added. The mixture was stirred at room temperature for 2 to 4 days or refluxed for one to 3 hours. A clear solution was usually formed. The formation of the acetal could be monitored by TLC. After the reaction was complete, the acid catalyst was destroyed by addition of either solid sodium hydrogen carbonate, or pyridine, or by partitioning between ethyl acetate and saturated sodium hydrogen carbonate solution. Finally, the solvent was removed by distillation. The products obtained were either syrups or solids, which could be recrystallized.

(B) N-Acetylation of ammonium salts

(i) Using acetic anhydride and triethylamine

A suspension of the ammonium salt (either hydrochloride or 4-methylbenzenesulphonate; 1 mmole) in ethanol (1 ml) was stirred rapidly, in an ice-bath, and treated successively with triethylamine (5 mmole) and acetic anhydride (2 ml). After stirring at ice-temperature for 30 minutes, the reaction mixture was allowed to warm up to room temperature for 2 hours. Then the mixture was partitioned between trichloromethane and water. The

organic layer was separated, washed, dried and evaporated to leave a crude product, which was purified by column chromatography.

(ii) Using acetic anhydride and 2N sodium hydroxide solution

A suspension of the ammonium salt (either hydrochloride or 4-methylbenzenesulphonate; 2 mmole) in ethanol (10 ml) was stirred rapidly, in an ice-bath, and treated successively with 2N sodium hydroxide solution (1 ml) and acetic anhydride (10 ml). After the addition, the cooling bath was removed and the reaction mixture was allowed to stir at ambient temperature for 2 hours. Then it was partitioned between trichloromethane and water. The organic layer was separated, washed, dried and evaporated to leave a crude product, which was purified by column chromatography.

(c) O-Acetylation of alcohols

The hydroxy compound (2 mmole) was dissolved in pyridine (50 ml) and then acetic anhydride (50 ml) was slowly added. The mixture was stirred in an ice-bath for 30 minutes and then at room temperature for one hour. Sometimes it was stored under refrigeration for 2 to 3 days. On occasions, the solvent was best removed under reduced pressure before an aqueous work-up. (In the sugar lactone series, a β-elimination occurred during the reaction). The product obtained was further purified by chromatography or by recrystallization.

(D) Azide displacement reactions on halides or sulphonates

(i) Using N,N-dimethylformamide as solvent

Sodium azide (90 mmole) was added to the halide or sulphonate (40 mmole) in N,N-dimethylformamide (40 ml). The mixture was heated in an oil-bath, at 100^{o}, for 4 to 6 hours. After cooling, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, thoroughly washed, dried and evaporated to leave the crude product as an oil, which was purified on a silica gel column.

(ii) Using aqueous 2-propanone as solvent

A solution of sodium azide (5 mmole) in water (2 ml) was added to a solution of the sulphonate (4 mmole) in 2-propanone (4 ml). The mixture was refluxed for 10 hours. TLC showed that the reaction was complete. Thus the mixture was evaporated to dryness. The residue was taken up with trichloromethane and washed thoroughly. The organic layer was separated, dried and evaporated to give a crude product, which was purified by column chromatography.

(E) N-Benzoylation of amines and ammonium salts

A solution or suspension of the amine or ammonium salt (1.0 mmole) in dichloromethane or trichloromethane (3 ml) was stirred rapidly, cooled in an ice-bath, and treated, successively, with benzoyl chloride (1.2 mmole)

and triethylamine (2.4 mmole). (In the case of a suspension, the solid gradually dissolved and a solution was formed). After stirring at ice temperature for 15 minutes, the cooling bath was removed and the mixture was allowed to stir at room temperature for a further one hour. Then the solvent was removed and the residue was triturated with ethyl acetate. The solid was filtered and the filtrate was evaporated to leave a crude product. The required amide was usually isolated as a solid after careful chromatography. Sometimes a gum or syrup was obtained.

(F) O-Benzoylation of alcohols

Benzoyl chloride (4.4 mmole) was added to a solution of the alcohol (4 mmole) in dichloromethane or trichloromethane (5 ml). The mixture was stirred in an ice-bath and triethylamine (4.66 mmole) was added, dropwise. The resulting solution was stirred at that temperature for 15 minutes and then at ambient temperature for a further 30 to 60 minutes. The solvent was removed under reduced pressure and the residue was triturated with ethyl acetate, giving a solid which was filtered. The filtrate was evaporated to leave a crude product, which was purified on a silica gel column.

(G) Epoxidation of alkenes

The alkene (27 mmole) was dissolved in dichloromethane (62 ml) and a solution of 3-chlorobenzenecarboperoxoic acid (121 mmole) in dichloromethane (18 ml) was added.

The mixture was stirred at room temperature for 3 to 5 days. Then an aqueous solution of sodium metabisulphite was added to the reaction mixture to destroy the excess oxidant. The organic layer was separated, washed with saturated sodium hydrogen carbonate solution, water, dried and evaporated to leave a crude product, which was purified by chromatography.

(H) The reaction of epoxides with diethyl 2-sodiopropanedioate

Ethanol (16 ml) was slowly added to 50% sodium hydride (27 mmole) giving a clear solution (ca. 30 minutes). Diethyl propanedioate (20 mmole) was added, dropwise. A cloudy solution was obtained. After stirring for 30 minutes at room temperature, the epoxide (13 mmole) was added, in portions. After the addition, the mixture was stirred at room temperature for 3 days (or refluxed overnight). The resulting brown mixture was acidified with dilute hydrochloric acid and then extracted with ethyl acetate. The extract was washed, dried and evaporated to afford a crude product, which was further purified by chromatographic means.

(I) Preparation of aldehyde hydrazone derivatives

The aldehyde (5 mmole) was dissolved in ethanol (17 ml) and 2,4-dinitrophenylhydrazine (5 mmole) was added. The mixture was heated under reflux and glacial acetic acid (0.5 ml) was added. After refluxing for 3 hours, TLC analysis of the reaction mixture indicated

that the reaction was complete. The reaction mixture was cooled in an ice-bath and orange coloured crystals gradually deposited. (Some hydrazones were brown or reddish-brown). The solid was filtered, washed with ethanol and dried in vacuo. Further purification was achieved by either recrystallization or chromatography.

(J) Hydrogenation of azides, nitriles, nitroalkanes and pyridines

All azides (including one allylic azide), cyanides and nitro compounds were reducible by 10% Pd-on-charcoal. However, it was necessary to use Adams' catalyst for the reduction of pyridines. The following reduction of compound (232) is typical:

10% Palladium-on-charcoal (1.42g; the same weight as azides) was added to a mixture of the azide (10.05 mmole) in ethanol (120 ml) and 2N hydrochloric acid (6 ml). The mixture was shaken under hydrogen in a Parr hydrogenator for 2 hours. (There were no volume change for azide reductions. However, in the case of nitriles, nitro compounds and pyridines, the reaction could be stopped, when the uptake of hydrogen became very slow and the expected amount of hydrogen had been absorbed). After degassing, the suspension was filtered through kieselguhr. The filtrate was evaporated to give the required ammonium chloride. Products were characterized as the corresponding amides of either acetic acid or benzoic acid.

(K) Singlet oxygenation of furans and subsequent reduction of the resulting endoperoxides

The furan (9 mmole) was dissolved in dichloromethane (150 ml) and a catalytic amount of methylene blue in methanol (2 ml) was added. Dry oxygen was bubbled through the mixture while it was cooled to -78^{o}. Then the mixture was irradiated with a 500W photo-flood light. The reaction was monitored by the disappearance of the starting material on TLC. Reaction was found to be complete after 30 minutes. The mixture was then transferred to a round-bottom flask and stirred rapidly. A solution of sodium tetrahydridoborate (28 mmole) in methanol (30 ml) was slowly added to the above mixture. Then the mixture was allowed to warm up to room temperature and stirred for 3 days. The excess reducing agent was destroyed by the addition of dilute hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed, dried and evaporated to leave the crude diol, which was derivatized as the corresponding dibenzoate.

(L) O-Sulphonation of alcohols

(i) Using triethylamine as base

The alcohol (4 mmole) was dissolved in ethyl acetate or tetrahydrofuran (5 ml) and stirred in an ice-bath. To this was added 4-methylbenesulphonyl chloride (5 mmole). The mixture was stirred rapidly and triethylamine (5 mmole) was added, slowly. After the addition, the reaction mixture was stirred in an ice-bath for a

further 15 minutes and then at ambient temperature for 30 to 60 minutes. The solid (triethylammonium chloride) was filtered. The filtrate was evaporated to leave a crude product, which was chromatographed to afford the pure sulphonate, usually a solid.

(ii) Using pyridine as solvent and base

A clear solution of the alcohol (6 mmole) in pyridine (10 ml) was stirred at -20° and 4-methylbenzene-sulphonyl chloride (13 mmole) was added, in one batch. A suspension was slowly formed. The mixture was stirred at this temperature for 3 hours. Then it was stored under refrigeration for 3 to 4 days. The mixture was slowly poured into stirred ice. The resulting white crystals were collected and dried *in vacuo* to yield the sulphonate. In one case a β-elimination occurred during the reaction. Further purification was by either recrystallization or chromatography.

(M) Synthesis of benzyloxycarbonyl (Z)-protected amino compounds

The amine (15 mmole) and sodium hydrogen carbonate (1 g) in benzene (10 ml) was stirred in an ice-bath and carbonochloridic acid phenylmethyl ester (2 ml) was added, dropwise. After the addition, the mixture was stirred at this temperature for 30 minutes and then at room temperature for a further 30 minutes. The reaction mixture was partitioned between ethyl acetate and water.

The organic layer was separated, washed, dried and evaporated to leave a crude product, which was purified by silica gel chromatography.

Preparations leading to β-aminomethyl-γ-butyrolactone salts (120)

1,3-Bis (acetyloxy)-2-propanone (109)

The method reported by Bentley and McCrae[149] was used. The acetylation gave the title compound as colourless needles (23.70g, 0.14mole, 81%);

m.p. 46-47^{o} (benzene-petrol ether 40-60^{o}) (lit.[149] m.p. 46-47^{o});

υ_{max} (Nujol) 1762 (acetate) and 1738 cm^{-1} (ketone C=O);

δ_{PMR} (100 MHz ; $CDCl_3$) 2.02 (6H, 2xs, 2xC$\underline{H}_3$) and 4.53 (4H, 2xS, 2xC$\underline{H}_2$);

δ_{CMR} (15 MHz; $CDCl_3$) 20.3 ($\underline{C}H_3$), 66.4 ($\underline{C}H_2$), 170.4 (acetate $\underline{C}$=O) and 198.3 (ketone $\underline{C}$=O);

G.C. at 160^{o}: Rt = 0.8 min.; procedure I;

TLC : Rf = 0.65 (solvent system A) and Rf = 0.2 (solvent system I).

Diethyl ethoxycarbonylmethylphosphonate (112)

The preparation was carried out according to the method described by Wolinsky and Erickson.[151] The reaction afforded the title ester as a colourless oil (7.90g, 35.20mmole, 71%);

b.p. 96^{o}/0.2 mm Hg, [lit.[151] b.p. 109-109.5^{o} (0.8 mm)];

υ_{max} (film) 1735 (C=O), 1270 (P=O) and 1040 cm^{-1} (P-O-C);

δ_{PMR} (100 MHz ; $CDCl_3$) 1.22 (3H, t, $\underline{J}$ = 7.6 Hz, O=COCH$_2$C$\underline{H}_3$), 1.32 (3H, t, $\underline{J}$ = 7.6 Hz, 2x OCH$_2$C$\underline{H}_3$), 2.83

(2H, d, $\underline{J}$ = 20 Hz, $PC\underline{H}_2$), 4.00 (2H, q, $\underline{J}$ = 7.6 Hz, $O{=}COC\underline{H}_2$), 4.30 (2H, q, $\underline{J}$ = 7.6 Hz, 2x $OC\underline{H}_2$);

δ_{CMR} (15 MHz; $CDCl_3$) 14.0 ($O{=}COCH_2\underline{C}H_3$), 16.0 and 16.5 (2 x $OCH_2\underline{C}H_3$, due to 2 x non-equivalent ethyls), 29.9 and 38.9 ($P{-}\underline{C}H_2$, doublet due to P-C coupling), 61.5 ($O{=}CO\underline{C}H_2CH_3$), 62.5 and 62.9 (2 x $O\underline{C}H_2$, due to 2 non-equivalent ethyls), 165.8 and 166.2 (2 x $\underline{C}{=}O$, due to P-C-C coupling);

G.C. at 160°: Rt = 1.1 minutes; procedure I;

TLC : Rf = 0.25 (solvent system I).

Ethyl 4-acetoxy-3-(acetoxymethyl)-2-butenoate (114)

Diethyl ethoxycarbonyl-methylphosphonate (2.51 g, 0.011 mole) was added dropwise, to a suspension of 80% sodium hydride (333 mg, 0.011 mole) in dry tetrahydrofuran (20 ml), under a blanket of nitrogen, keeping the temperature below 35°. Evolution of gas began immediately. After the gas evolution stopped, (ca. one hour), a solution of 1,3-bis(acetyloxy)-2-propanone (2.00 g, 0.011 mole) in tetrahydrofuran (2.5 ml) was added, dropwise. A brown solution was formed immediately, and a gelatinous precipitate formed very quickly. After stirring for a further hour, the reaction mixture was poured into a large excess of water and then extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to leave a brown oil. The crude product was purified on a silica gel column, eluting with a mixture of ethyl acetate and petrol ether 40-60° (1:2) (solvent system J). The fractions containing the

required product were combined and evaporated to leave the title ester as a pale yellow oil (0.67 g, 2.75 mmole, 47%);

υ_{max} (film) 1750 (acetate carbonyl), 1720 (ester) and 1615 cm^{-1} (C=C);

δ_{PMR} (100 MHz; $CDCl_3$) 1.32 (3H, t, $\underline{J}$ = 7.6 Hz, $OCH_2C\underline{H}_3$) 2.09 and 2.16 (6H, 2xs, $2xC\underline{H}_3CO$), 4.28 (2H, q, $\underline{J}$ = 7.6 Hz, $OC\underline{H}_2$), 4.80 (2H, bs, $=C-C\underline{H}_2$, cis to carbonyl $C\underline{H}_2$) and 538 (2H, bs, $=C-C\underline{H}_2$, trans to carbonyl $C\underline{H}_2$), and 6.14 (1H, t, =-H, $\underline{J}$ = 2 Hz);

δ_{CMR} (15 MHz; $CDCl_3$), 14.2 ($OCH_2\underline{C}H_3$), 20.7 ($\underline{C}H_3CO$), 60.7 ($O\underline{C}H_2CH_3$), 61.1 $C=C-\underline{C}H_2$, cis to carbonyl) and 63.8 ($=C-\underline{C}H_2$, trans to carbonyl), 119.1 ($=\underline{C}-CO$), 148.9 ($CH_2\underline{C}=C$), 165.5 (ester $\underline{C}=O$, $\underline{C}O_2CH_2CH_3$), 170.5 and 170.8 ($2xCH_3\underline{C}=O$);

[Found: C, 53.7; H, 6.2; $C_{11}H_{18}O_6$ (246.3) requires C, 54.1; H, 6.6%];

G.C. at 160° : Rt = 2.4 min.; procedure I;

TLC: Rf = 0.5 (solvent system I).

Ethyl 4-acetoxy-3-[(acetoxy)methyl]butanoate (115)

10% Palladium-on-charcoal (3.6 g) was added to a solution of ethyl 4-acetoxy-3-[(acetoxy)methyl]-2-butenoate (4.00 g, 16.5 mmole) in ethyl acetate (80 ml). The mixture was shaken with hydrogen, at atmospheric pressure and temperature until the uptake was sluggish (total uptake was 620 ml in 5 minutes). After degassing, the suspension was filtered through a cake of kieselguhr. The filtrate was evaporated to leave the title compound

as a colourless oil (3.43 g, 13.9 mmole, 84%);

υ_{max} (film) 2900-2990 (CH) and 1740 cm^{-1} (ester);

δ_{PMR} (100 MHz; $CDCl_3$) 1.32 (3H, t, $\underline{J}$ = 7.6 Hz, OCH_2-$C\underline{H}_3$), 2.08 (6H, 2xs, $2xC\underline{H}_3CO$), 2.20-2.80 (3H, m, $O{=}C\underline{H}_2C\underline{H}$), 4.15 (4H, d, $\underline{J}$ = 6 Hz, $OC\underline{H}_2$) and 4.21 (2H, q, $\underline{J}$ = 7.6 Hz, $OC\underline{H}_2CH_3$);

δ_{CMR} (15 MHz; $CDCl_3$) 14.2 ($OCH_2\underline{C}H_3$), 20.7 ($\underline{C}H_3C{=}O$), 33.5 ($\underline{C}H_2CO_2$), 34.5 ($\underline{C}H$), 60.8 ($O\underline{C}H_2CH_3$), 63.87 ($O\underline{C}H_2CH$), 171.1 ($CH_3\underline{C}{=}O$) and 171.9 ($\underline{C}O_2CH_2CH_3$);

[Found: C, 53.6; H, 7.6; $C_{11}H_{18}O_6$ (246.2) requires C, 53.7; H, 7.4%];

G.C. at 160^o: Rt = 2.18 min., procedure I;

TLC: Rf = 0.85 (solvent system H).

<u>Ethyl 4-hydroxy-3-hydroxymethylbutanoate (116)</u>

A 0.39 N sodium ethoxide in ethanol (15.6 ml, 6.09 mmole) was added, dropwise, to a solution of ethyl 4-acetyloxy-3-[(acetyloxy)methyl]butanoate (497 mg, 2.02 mmole) in ethanol (5.0 ml), with rapid stirring. After the addition, the pale yellow solution was stirred at room temperature for 30 minutes. Then Dowex-50W-X8 (2.1 g) was added. The mixture was stirred for a further 20 minutes and then the resin was filtered. The filter-cake was washed thoroughly with ethanol. The combined organic layer was evaporated to leave the <u>title ester</u> as a colourless oil (246 mg, 1.54 mmole, 76%);

υ_{max} (film) 3400 (OH), 1760 (lactone) and 1740 cm^{-1} (ester);

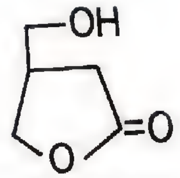
δ_{PMR} (60 and 100 MHz, D_2O) 1.25 (3H, t, $\underline{J}$ = 7.6 Hz,

$OC\underline{H}_2C\underline{H}_3$), 2.05-3.2 (3H, m, $C\underline{H}C\underline{H}_2CO_2Et$), 3.6 (4H, d, $\underline{J}$ = 6 Hz, $2xHOC\underline{H}_2CH$), and 4.15 (2H, q, $\underline{J}$ = 7.6 Hz, $OC\underline{H}_2CH_3$); and a small amount of minor signals, probably due to the lactone ;

TLC: Rf = 0.75 (solvent system P).

N.B. This product was not very pure as judged by the integral on the ethyl signals which were less than expected, comparing with the other signals. This was used in the next stage without further purification.

Dihydro-4-(hydroxymethyl)-2-(3H)-furanone (117)



(117)

The following two methods were used.

(A) 4-Methylbenzenesulphonic acid as catalyst

4-Methylbenzenesulphonic acid monohydrate (33 mg) was added to a solution of ethyl 4-hydroxy-3-hydroxymethylbutanoate (69 mg, 0.43 mmole) in a mixture of ethanol (6.0 ml) and water (60 ml). An exothermic reaction occurred. The reaction was then refluxed for 30 minutes. After cooling the solvent was evaporated to leave a yellow oil. The crude product was purified on a silica gel column, eluting with a mixture of ethanol and trichloromethane (1:4). Fractions containing the required

product were combined and evaporated to leave the title hydroxy compound as a pale yellow oil (56 mg, 0.47 mmole, 112%);

υ_{max} ($CHBr_3$) 3375 (OH) and 1765 cm^{-1} (lactone);

δ_{PMR} (60 MHz; D_2O) 2.0-3.2 (3H, m, $C\underline{H}C\underline{H}_2CO$), 3.6 (2H, d, $\underline{J}$ = 6 Hz, $C\underline{H}_2OH$), 4.0-4.6 (2H, m, $OC\underline{H}_2$);

TLC: Rf = 0.6 (solvent system B).

N.B. Product was contaminated with 4-methylbenzenesulphonic acid (ca. 15%).

(B) Trifluoroacetic acid as catalyst

Trifluoroacetic acid (0.38 ml) was added to a solution of ethyl 4-hydroxy-3-hydroxymethylbutanoate (190 mg, 1.19 mmole) in water (3.4 ml). After standing at room temperature for 30 minutes, the solvent was removed to give the title compound as a light yellow oil (198 mg, 1.71 mmole, 144%);

υ_{max} (film) 3410 (OH) and 1770 cm^{-1} (lactone);

δ_{PMR} (100 MHz; D_2O) 2.1-3.2 (3H, m, $C\underline{H}C\underline{H}_2CO$), 3.62 (2H, d, $\underline{J}$ = 6 Hz, $C\underline{H}_2OH$), 4.2-4.32 (1H, m, $\underline{H}CHO$) and 4.48-4.8 (1H, m, $HC\underline{H}O$);

δ_{CMR} (15 MHz; D_2O) 30.5 ($-\underline{C}HCH_2$), 36.1 ($\underline{C}H_2CO$), 62.1 ($HO\underline{C}H_2$), 71.85 ($\underline{C}H_2O-$) and 181.5 ($\underline{C}=O$);

TLC: Rf = 0.6 (solvent system B).

N.B. The product was not very pure and was contaminated by some residual water (ca. 40%), which could be seen as an "inflated" HOD signal in the PMR spectrum (mea-

sured in D_2O). Furthermore there was no other contaminants in the product as judged by its ^{1}H-NMR (Spectrum P-3) and C-13 NMR (Spectrum C-3) spectra. However, this residual water could not be removed azeotropically.

Dihydro-4-[[(methanesulphonyl)oxy]methyl]-2(3H)-furanone (118b)

(A) The general procedure [(L), conditions (ii)] for O-sulphonation was used. Thus the title compound was prepared from a solution of dihydro-4-(hydroxymethyl)-2(3H)-furanone (74 mg, 0.64 mmole) in pyridine as a brown oil (92 mg, 0.47 mmole, 74%);

υ_{max} (film) 1770 (lactone), 1325 and 1165 cm^{-1} (SO_2); δ_{PMR} (60 MHz ; $CDCl_3$) 2.0-3.2 (3H, m, C$\underline{H}$C$\underline{H}_2$CO), 3.1 (3H, s, C$\underline{H}_3SO_2$), 4.39 (2H, d, J = 6 Hz, OC$\underline{H}_2$) and 4.05-4.8 (2H, m, C$\underline{H}_2SO_2$);

TLC: Rf = 0.9 (solvent system C) and Rf = 0.55 (solvent system H).

N.B. The product still contained a small amount of pyridine.

(B) The general method (L) for O-sulphonation using triethylamine as base [conditions (i)] was used. Thus the title lactone was obtained from dihydro-4-(hydroxymethyl)-2(3H)-furanone (149 mg, 1.28 mmole) as a yellow oil (300 mg, 1.28 mmole, 100%);

ν_{max} ($CHBr_3$) as reported previously;

δ_{PMR} (100 MHz; $CDCl_3$) 2.3-3.3 (3H, m, C$\underline{H}$C$\underline{H}_2$CO), 3.15 (3H, s, C$\underline{H}_3SO_2$), 4.39 (2H, d, $\underline{J}$ = 6 Hz, OC$\underline{H}_2$) and 4.1-4.8 (2H, m, C$\underline{H}_2OSO_2$);

δ_{CMR} (15 MHz; $CDCl_3$) 30.2 (-$\underline{C}$HCH_2), 34.5 (C$\underline{H}_2$CO), 37.3 ($\underline{C}H_3SO_2$), 68.7 ($\underline{C}H_2OSO_2$), 69.4 ($\underline{C}H_2O$-) and 175.7 ($\underline{C}$=O);

Mass spectrum: M/Z 194 (M^+), $C_6H_{10}O_5S$ requires 194.2;

TLC: Rf = 0.9 (solvent system P) and Rf = 0.55 (solvnet system H).

<u>4-(Azidomethyl)dihydo-2-(3H)-furanone (119)</u>

(A) General procedure (D) for azide displacement in N,N-dimethylformamide as solvent [conditions (i)] was used. Thus dihydro-4-[[(methanesulphonyl)oxy]methyl]-2(3H)-furanone (61 mg, 0.43 mmole) reacted with sodium azide to give the <u>title azide</u> as a brown oil (15 mg, 0.11 mmole, 26%);

ν_{max} (film) 2100 (N_3) and 1775 cm^{-1} (lactone);

δ_{PMR} (60 MHz; $CDCl_3$) 2.0-3.2 (3H, m, C$\underline{H}$C$\underline{H}_2$CO), 3.5 (2H, d, $\underline{J}$ = 6 Hz, C$\underline{H}_2N_3$) and 3.95 to 4.65 (2H, m, C$\underline{H}_2$O);

TLC: Rf = 0.65 (solvent system H).

N.B. The sample was contaminated with N,N-dimethylformamide.

(B) Using general procedure (D) for azide displacement

in aqueous 2-propanone [conditions (ii)], dihydro-4-[[(methanesulphonyl)oxy]methyl]-2(3H)-furanone (0.79 g, 4.1 mmole) reacted with sodium azide to give the title compound as a brown oil (425 mg, 73%);

υ_{max} (film) as reported above;

δ_{PMR} (100 MHz; $CDCl_3$) 2.1-3.2 (3H, m, C$\underline{H}$C$\underline{H}_2$CO), 3.5 (2H, d, $\underline{J}$ = 6 Hz, C$\underline{H}_2N_3$) and 4.1-4.8 (2H, m, C$\underline{H}_2$O);

δ_{CMR} (15 MHz; $CDCl_3$) 31.3 (-$\underline{C}$HCH$_2$), 34.7 ($\underline{C}H_2$CO), 52.5 ($\underline{C}H_2N_3$), 70.1 ($\underline{C}H_2$O) and 175.9 ($\underline{C}$=O);

Mass spectrum: M/Z 141 (M^+), $C_5H_7N_3O_2$ requires 141.1;

TLC: Rf = 0.65 (solvent system H)

4-(Aminomethyl)dihydro-2(3H)-furanone, hydrochloride (120a)

(A) Using aqueous HCl and the azide (119)

The product was prepared by the hydrogenolysis [general procedure (J)] of 4-(azidomethyl)dihydro-2(3H)-furanone (210 mg, 1.49 mmole), in the presence of 1 N aqueous hydrochloric acid. The title hydrochloride was obtained as a light brown hygroscopic solid (187 mg, 1.24 mmole, 94%);

υ_{max} (film) 3700 to 2100 ($\overset{+}{N}H_3$ and OH) and 1760 cm^{-1} (lactone);

δ_{PMR} (60 MHz; D_2O) 2.1-3.2 (3H, m, C$\underline{H}$C$\underline{H}_2$CO), 3.5-3.9 (2H, m, C$\underline{H}_2NH_2$), 4.0-4.6 (2H, m, C$\underline{H}_2$O);

TLC: Rf = 0 (solvent system H).

(B) Using aqueous HCl and the nitro compound (182)

The general procedure (J) was used for the hydrogenolysis of dihydro-4-(nitromethyl)-2(3H)-furanone (2.0 g, 13.8 mmole), in the presence of aqueous hydrochloric acid solution. The title hydrochloride was isolated as a brown syrup (2.18 g, monohydrated, 13.8 mmole, 100%); NMR and IR spectra were identical with those reported in method (A).

(C) Using aqueous HCl and the azido-butenolide (202)

The title hydrochloride was prepared according to general procedure (J) for the hydrogenolysis of 4-(azidomethyl)-2(5H)-furanone (1.5 g, 10.7 mmole). The product was isolated as a gummy solid (2.44 g, tetrahydrate, 10.7 mmole, 100%); Ir spectrum was identical with those of (A) and (B);

δ_{PMR} (200 MHz; D_2O and TSP) 2.5 and 2.58 (1H, dd, J = 7 and 7 Hz, $\underline{H}$CHCO), 2.85 and 2.95 (1H, dd, J = 8 and 8 Hz, HC$\underline{H}$CO), 3.0 to 3.2 (1H, m, C$\underline{H}CH_2$CO), 3.18-3.25 (2H, dd, J = 1.5 and 3 Hz, N$C\underline{H}_2$), 4.2 amd 4.25 (1H, dd, J = 6 Hz, $\underline{H}$CHO) and 4.6 and 4.64 (1H, dd, J = 7.5 amd 7.5 Hz, HC$\underline{H}$O);

δ_{CMR} (15 MHz; D_2O and dioxan) 32.81 ($\underline{C}HCH_2$CO), 34.1 ($\underline{C}H_2$CO), 41.79 (N$\underline{C}H_2$), 72.33 (O$\underline{C}H_2$) and 180.98 ($\underline{C}$=O);

TLC: Rf = 0 (solvent system H).

4-(Aminomethyl)dihydro-2(3H)-furanone, 4-methylbenzenesulphonic acid salt (120b)

The hydrogenolysis [general procedure (J)] of 4-(azidomethyl)dihydro-2(3H)-furanone (258 mg, 1.89 mmole)

in the presence of 4-methylbenzenesulphonic acid monohydrate gave the title salt as a light yellow hygroscopic solid (53 mg, 1.85 mmole, 98%);

ν_{max} (Nujol) 3700 to 2100 ($\overset{+}{N}H_3$ and OH), 1780 (lactone), 1310 and 1120 cm^{-1} (S=O);

δ_{PMR} (100 MHz; $CDCl_3$ + DMSOd^6) 2.37 (3H, s, Ar$C\underline{H}_3$), 2.15-2.90 (3H, m, $C\underline{H}C\underline{H}_2CO$), 3.30-3.7 (2H, m, $C\underline{H}_2NH_2$), 3.7-4.05 (1H, m, $\underline{H}CHO-$), 4.05-4.3 (1H, m, $HC\underline{H}O-$);

δ_{CMR} (15 MHz; D_2O and dioxane) 21.1 (Ar$\underline{C}H_3$), 32.6 ($-\underline{C}HCH_2$), 33.9 ($\underline{C}H_2CO$), 42.9 ($\underline{C}H_2N$), 72.07 ($\underline{C}H_2O$), 126.1 (CH_3-), 130.2 (CH_3-), 140.5 (CH_3-), 143.2 (-S) and 180.6 ($\underline{C}$=O);

TLC: Rf = 0 (solvent system H).

4-(Acetylamino)dihydro-2(3H)-furanone (121)

(A) Using general procedure [(B) conditions (i)] for the acylation of ammonium salts

The treatment of 4-(aminomethyl)dihydro-2(3H)-furanone, hydrochloride (180 mg, 1.19 mmole) with acetic anhydride and then with triethylamine gave the title amide as a brown oil (52 mg, 0.32 mmole, 27%);

ν_{max} (film) 3400 (NH), 1775 (lactone), 1655 and 1550 cm^{-1} (CONH);

TLC: Rf = 0.57 (solvent systme G).

(B) Using general procedure [(B), conditions (ii)] for the preparation

The reaction of 4-(aminomethyl)dihydro-2(3H)-furanone,

4-methylbenzenesulphonic acid salt (566 mg, 1.97 mmole) with acetic anhydride, in the presence of 2 N aqueous sodium hydroxide solution, gave a crude product which was purified by silica gel column chromatography to afford the title compound as an oil (182 mg, 1.16 mmole, 59%);

υ_{max} (film) 3420 (NH), 1758 (lactone), 1640 and 1540 cm^{-1} (CONH);

δ_{PMR} (100 MHz; $CDCl_3$) 2.02 (3H, s, $C\underline{H}_3CON$), 2.15-3.2 (3H, m, $C\underline{H}C\underline{H}_2CO$), 3.3-3.6 (2H, m, $C\underline{H}_2N$), 4.1-4.8 (2H, m, $C\underline{H}_2O$-) and 5.8 (1H, bs, $CON\underline{H}$);

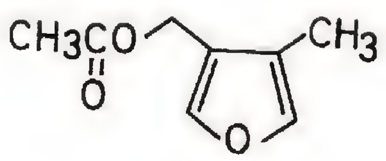
δ_{CMR} (50 MHz; $DMSOd^6$) 20.4 ($\underline{C}H_3$), 31.7 ($\underline{C}HCH_2CO$), 33.3 ($\underline{C}H_2CO$), 43.0 ($N\underline{C}H_2$), 70.8 ($\underline{C}H_2O$), 169.1 (amide $\underline{C}$=O) and 177.2 (lactone $\underline{C}$=O);

[Found: C, 38.5; H, 8.21; N, 6.2; $C_7H_{11}NO_3$. 3.5 H_2O (220.2) requires C, 38.2; H, 8.2; N, 6.4%];

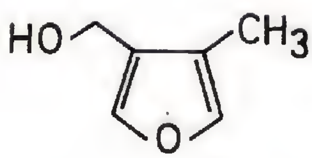
TLC: Rf = 0.57 (solvent system G).

N.B. According to the analyst, this compound gained weight during the weighing process.

3-Methyl-4-[(acetyloxy)methyl]furan (153) and 3-methyl-4-(hydroxymethyl)furan (154)



(153)



(154)

A mixture of 1,3-dihydroxy-2-propanone (5.0 g, 55 mmole), diethyl propanedioate (7.95 g, 49.5 mmole) and ammonium acetate (3.4 g, 44 mmole) in equal amount of acetic acid (16 ml) and benzene (16 ml) was heated on a Dean-Stark apparatus for a total of 9 hours. After cooling the dark-brown mixture was concentrated to leave a reddish-brown oil. The crude product was put into a slurry silica gel column (100 g), eluting with a mixture of petroleum ether 40-60^{o} and ethyl acetate (1:1; 1:2), ethyl acetate (neat), a mixture of ethyl acetate and methanol (1:5) and finally methanol (neat). Fractions 10 to 13 were combined and evaporated to give the <u>title acetate</u> as a reddish-brown oil (444 mg, 2.88 mmole, 5.8%);

υ_{max} (film) 3005 to 2930 (aromatic and aliphatic C-H stretch), 1740 (ester C=O), 1537, 1490 and 1439 (ring C$\overset{-}{-}$C stretch), 1220, 1160, 1030 and 882 cm^{-1} (furan);

δ_{PMR} (100 MHz; $CDCl_3$) 2.15 (3H, s, $C\underline{H}_3C{=}O$), 2.55 (3H, s, $C\underline{H}_3Ar$), 5.05 (2H, s, $C\underline{H}_2$-O), 8.22 and 8.3 (2H, two apparent s, two furan protons);

δ_{CMR} (15 MHz; $CDCl_3$) 20.8 ($\underline{C}H_3C{=}O$), 21.3 ($\underline{C}H_3Ar$), 64.7 ($\underline{C}H_2$-O), 143.03 and 144.3 ($\underline{C}$-2 and $\underline{C}$-5 of furan), 148.3 and 153.8 ($\underline{C}$-3 and $\underline{C}$-4 of furan) and 170.9 (ester $\underline{C}$=O);

Mass spectrum: M/Z 154 (M^+), $C_8H_{10}O_3$ requires 154.2;

G.C. (column temperature 50 to 20^{o} at 10^{o} per minute): Rt = 6.8 min, indicating about 80^{o} pure; procedure 2;

TLC: Rf = 0.45 (solvent system J).

Fractions 22 to 26 were combined and evaporated to

leave the <u>title alcohol</u> as a black gum (435 mg, 3.9 mmole, 7.9%);

υ_{max} (film) 360 to 3250 (OH), 3003 to 2925 (aromatic and aliphatic C-H stretch), 1540, 1485 and 1420 (ring C⩵C stretch); 1280, 1201, 1110, 1080 and 930 cm^{-1} (furan);

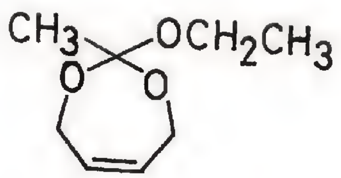
δ PMR (100 MHz; $CDCl_3$) 2.62 (3H, s, $C\underline{H}_3Ar$), 4.3 (1H, bs, disappeared after deuterated with D_2O, $O\underline{H}$), 4.92 (2H, s, $C\underline{H}_2$-O), 8.59 and 8.72 (2H, two apparent s, two furan protons);

δ CMR (15 MHz; $CDCl_3$) 21.2 ($\underline{C}H_3C{=}O$), 62.8 ($\underline{C}H_2$-O), 142.1 and 143.4 ($\underline{C}$-2 and $\underline{C}$-5 of furan), 152.0 152.9 ($\underline{C}$-3 and $\underline{C}$-4 of furan);

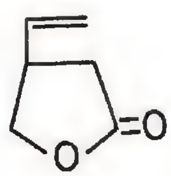
mass spectrum : M/Z 110 (M^+), $C_6H_6O_2$ requires 110.1;

TLC : Rf = 0.14 (solvent system J).

<u>Preparation of 2-methyl-2-ethoxy-1,3-dioxacyclohept-5-ene (170) and 4-ethenyldihydro-2(3H)-furanone (169)</u>



(170)



(169)

1,4-Benzenediol (1.76g) was added to a mixture of (Z)-2-butene-1,4-diol (165 ml, 0.2 mole) and 1,1,1-triethoxyethane (81.5 ml, 0.4 mole). The mixture was heated at 140-150° for 6 hours and the excess 1,1,1-triethoxyethane and (Z)-2-butene-1,4-diol and ethanol which was produced during the course of reaction were removed by a Dean-Stark set-up, while heating at 150°. Then the mixture

was heated for a further 6 hours. The residue was distilled at 45 mm Hg to give first residual 1,1,1-triethoxyethane, at 80-96^{o} (11.44 g), and then the <u>title cyclohep-tene</u> (13.53 g, 85.6 mmole, 43%);

b.p. 100-106^{o} (45 mm Hg);

υ_{max} (film) 1640 (C=C), 1200, 1150 and 1030 cm^{-1} (C-O-C);

δ_{PMR} (200 MHz; $CDCl_3$) 1.28 (3H, t, $\underline{J}$ = 7.6 Hz, $OCH_2C\underline{H}_3$), 1.58 (3H, s, $C\underline{H}_3$), 3.6 (2H, q, $\underline{J}$ = 7.6 Hz, $OC\underline{H}_2CH_3$), 4.18 4.48 (4H, 2 x collapsed d, $\underline{J}$ = 16 Hz, 2 x $C\underline{H}_2C$=), and 5.70 (2H, t, $\underline{J}$ = 2 Hz, 2 x $CH_2C\underline{H}$=);

δ_{CMR} (15 MHz; $CDCl_3$) 15.43 ($OCH_2\underline{C}H_3$), 19.08 ($\underline{C}H_3C$), 58.92 ($O\underline{C}H_2CH_3$), 61.52 (2 x $O\underline{C}H_2C$=), 116.28 ($CH_3\underline{C}$-O) and 129.17 (2 x $CH_2\underline{C}$=);

[Found: C, 58.3; H, 8.3 ; $C_8H_{14}O_3 \cdot 0.4H_2O$ (165.4) requires C, 58.1; H, 8.9%];

TLC: Rf = 0.8 (solvent system J).

The residue which could not be distilled over at this pressure was examined by NMR spectroscopy. This was proved to be a mixture of the vinyl ester, vinyl lactone and the catalyst. Thus the mixture was treated with trifluoroacetic acid (15 ml) and the resulting solution was left standing at room temperature for 2 days. Then the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed with water, saturated sodium hydrogen carbonate solution, water, dried and evaporated to leave a dark brown gum. The crude product was purified by column

chromatography, eluting with a mixture of petrol ether 40-60^o and ethyl acetate (2:1, 1:1) and finally ethyl acetate. Fractions containing the required product were combined and evaporated to leave the title vinyl lactone as a brown oil (2.37 g, 21.2 mmole, 11%);

υ_{max} (film) 1740 (lactone) and 1622 cm^{-1} (C=C);

δ_{PMR} (200 MHz; $CDCl_3$) 2.48 (1H, 2xd, $\underline{J}$ = 8 and 8 Hz, $\underline{H}$CHCO), 2.7 (1H, 2xd, $\underline{J}$ = 8 and 8 Hz, HC$\underline{H}$CO) 3.22 (1H, m, $\underline{H}CCH_2CO$), 4.03 (1H, 2xd, J = 8 and 8 Hz, $\underline{H}$CH-O), 4.46 (1H, 2xd, J = 8 and 8 Hz, HC$\underline{H}$-O), 5.1-5.28 (2H, m, $\underline{H}_2C{=}C$) and 5.8 (1H, m, =C$\underline{H}$-);

δ_{CMR} (15 MHz; $CDCl_3$) 33.98 ($\underline{C}HCH_2CO$), 39.58 ($\underline{C}H_2CO$), 72.33 ($-O\underline{C}H_2$), 117.44 ($CH_2{=}\underline{C}H-$), 135.80 ($\underline{C}H_2{=}C-$) and 177.14 ($\underline{C}{=}O$);

TLC: Rf = 0.25 (solvent system J).

Ozonolysis of 4-ethenyldihydro-2(3H)-furanone (169) and reduction of the resulting aldehyde with sodium tetrahydridoborate

A solution of 4-ethenyldihydro-2(3H)-furanone (3.703 g, 33.10 mmole) in dichloromethane (120 ml) was cooled to -78^o and ozonized oxygen was bubbled through the solution for 2.5 h. A bluish solution was finally obtained. The excess ozone was blown off by passing nitrogen through the solution. Then dimethyl sulphide (2.4 ml, 33.10 mmole) was added to destroy the residual dissolved ozone. The mixture was allowed to warm up to room temperature and stirred for 1.5 days. Then the reaction mixture was diluted with ethyl acetate and washed with water. The

organic layer was separated, dried and evaporated to leave 4-formyldihydro-2(3H)-furanone (172) as a dark-brown gum.

The above prepared aldehyde was dissolved in methanol (50 ml) and stirred in an ice-bath. To this solution was added sodium tetrahydridoborate (1.324 g, 33.10 mmole), in portions. Gas evolution occurred immediately after the addition of the reducing agent. Then the reaction mixture was stirred at room temperature for one hour. The suspension was acidified to pH 2 and the clear light brown solution was evaporated to dryness. The residue was extracted with ethyl acetate. The organic layer was dried and evaporated to leave dihydro-4-(hydroxymethyl)-2(3H)-furanone (117) as a brown oil (3.843 g, 33.10 mmole, 100%).

IR and NMR (60 MHz) and TLC were similiar to that prepared by alternative method.

4-[(Benzoyloxy)methyl]dihydro-2(3H)-furanone (173)

The general procedure (F) for O-benzoylation of hydroxy compounds was used. Thus dihydro-4-(hydroxymethyl)-2(3H)-furanone was reacted with benzoyl chloride, in the presence of triethylamine, to give the title benzoate light brown oil (432 mg, 1.96 mmole, 60%);

υ_{max} (film) 1765 (lactone C=O) and 1710 cm^{-1} (ester C=O);

δ_{PMR} (200 MHz; $CDCl_3$) 2.42 and 2.51 (1H, 2xd, J = 8 Hz, HCHCO), 2.72 and 2.8 (1H, 2xd, J = 8 Hz, CHCO), 2.98-3.18

(1H, m, CHCH$_2$CO), 4.21 and 4.25 (1H, 2xd, J = 6 and 6 Hz, HCHO), 4.4 (2H, dABq, J = 6 and 6 Hz, CH$_2$OC(=O)Ph), 4.5 and 4.55 (1H, 2xd, J = 8 and 8 Hz, HCHO), 7.38-7.7 and 7.95-9.25 (5H, m, aromatic protons);

δ_{CMR} (15 MHz; CDCl$_3$) 31.11 (CHCH$_2$CO), 34.50 (CHCO), 65.10 (CH$_2$OCOPh), 70.37 (CH$_2$O, lactone), 128.7, 130.27 and 133.52 (aromatic carbon atoms), 166.40 (benzoate C=O) and 176.42 (lactone C=O);

[Found: C, 66.5; H, 5.9 ; $C_{12}H_{12}O_4$. 0.05 EtOAc (224.6) requires C, 66.0; H, 5.3%];

TLC: Rf = 0.31 (solvent system J).

3-Bromodihydro-2(3H)-furanone (180)

The title compound was prepared from butyrolactone (144) according to a literature procedure.[220] The yield of the light brown liquid was (46.3 g, 0.27 mole, 55%);

b.p. 95-99^o (4 mm Hg) [lit.[220] b.p. 125-127^o (13 mm)];

υ_{max} (film) 1780 cm^{-1} (lactone);

δ_{PMR} (200 MHz; CDCl$_3$) 2.38-2.58 (1H, m, HCHCHCO), 2.68-2.92 (1H, m, HCHCHCO) and 4.3-4.6 (3H, m, CHCO and CH$_2$O);

δ_{CMR} (15 MHz; CDCl$_3$) 33.78 (CH$_2$CHCO), 37.63 (CHCO), 67.12 (CH$_2$O) and 173.43 (lactone C=O);

TLC: Rf = 0.6 (solvent system Q).

2(5H)-Furanone (181)

The literature method[220] for the dehydrobromination of the bromide (180) was used to give the title unsaturated lactone as a very pale brown oil (3.7 g, 44.5 mmole, 71%);

b.p. 135-136^{o} (30 mm Hg) [lit.[220] b.p. 107-109^{o} (24 mm)];

υ_{max} (film) 1775 and 1740 cm^{-1} ($\Delta^{\alpha,\beta}$-butenolide);

δ_{PMR} (200 MHz; $CDCl_3$) 4.92 (2H, t, J = 1.5 Hz, CH_2O), 6.15 (1H, 2xt, J =2 and 2 Hz, CH_2-CH=) and 7.57 (1H, 2xt, J = 1.5 and 1.5 Hz, =CHCO);

δ_{CMR} (15 MHz; $CDCl_3$) 72.26 (CH_2O), 121.8 (=CHCO), 153.12 (CH_2-CH=) and 174.02 (C=O);

TLC: Rf = 0.7 (solvent system Q).

Dihydro-4-(nitromethyl)-2(3H)-furanone (182)

(A) Using tetrabutylammonium hydroxide as catalyst

A mixture of 2(5H)-furanone (0.5 g, 5.95 mmole), nitromethane (6 ml), dichloromethane (20 ml) and water (2 ml) was stirred rapidly and 40% aqueous tetrabutylammonium hydroxide solution (3.85 g, 5.95 mmole) was added, dropwise. The orange solution was stirred for 30 minutes. Then the mixture was partitioned between ethyl acetate and 0.5 N aqueous hydrochloric acid. After shaken, the organic layer decolourized. The organic layer was separated, washed with saturated sodium hydrogen carbonate solution, water, dried and evaporated to leave a light yellow oil. The crude product was purified by silica gel column chromatograph, eluting with a mixture of ethyl acetate and petrol ether 40-60^{o} (1:2 and then 1:1) and finally ethyl acetate. Fractions containing the required product were combined and evaporated to leave the title compound as a pale brown oil (260 mg, 1.79 mmole, 30%);

ν_{max} (film) 1770 (lactone), 1545 and 1350 cm^{-1} (NO_2);

δ_{PMR} (200 MHz; $CDCl_3$) 2.35 and 2.42 (1H, 2xd, J = 7 and 7 Hz, HCHCO), 2.80 and 2.92 (1H, 2xd, J = 9 and 9 Hz, CHCO), 3.24-3.58 (1H, m, $CHCH_2CO$), 4.18 and 4.22 (1H, 2xd, J = 6 and 6 Hz, HCHO), 4.59 and 4.62 (1H, 2xd, J = 7 and 7 Hz, HCHO) and 4.58 (2H, 2xd, J =7 and 7 Hz, NCH_2);

δ_{CMR} (15 MHz; $CDCl_3$) 31.57 ($CHCH_2CO$), 33.59 (CH_2CO), 70.25 (CH_2O), 76.30 (NCH_2) and 175.19 (C=O);

[Found: C, 41.4; H, 4.9; N, 9.7; $C_5H_7NO_4$ (145.1) requires C, 41.4; H, 4.9; N, 9.7%];

TLC: Rf = 0.8 (solvent system H).

(B) Using 18-crown-6 as catalyst

A mixture of 2(5H)-furanone (0.1 g, 1.19 mmole), 1,4,7,10,13,16-hexaoxacyclooctadecane (0.16 g, 0.6 mmole) and nitromethane (1.2 ml) in dichloromethane (10 ml) was stirred and anhydrous potassium carbonate (0.08 g, 0.6 mmole) was added. The mixture was stirred at room temperature for 4 days. Then it was partitioned between ethyl acetate and water. The organic layer was separated, washed, dried and evaporated to leave the title compound as a yellow oil (0.16 g, 1.1 mmole, 100%); this crude product was about 80% pure as judged by NMR spectroscopy and TLC evidence.

(C) From the open-chain analogue (188)

0.4 M Sodium ethoxide in ethanol (19.2 ml, 7.68 mmole) was added to a solution of ethyl 4-(benzoyloxy)-3-(nitromethyl)-butanoate (2.07 g, 6.42 mmole) in ethanol (16 ml).

After stirring at room temperature for 55 minutes, Dowex-50W-X8 resin (4.8 g) was added. The mixture was stirred for 20 minutes and then the resin was filtered. The filtrate was evaporated to leave a brown oil. This residue was suspended in water (1.0 ml) and trifluoroacetic acid (4.0 ml) was added. The resulting solution was allowed to stand at room temperature for 30 minutes. Then the solvent was removed to leave brown syrup, which was examined by NMR spectroscopy. It contained only about 10% of the required product in this crude form.

Thus the above mixture was dissolved in tetrahydrofuran (5 ml) and a solution of sodium hydroxide (0.51 g, 12.8 mmole) in water (10 ml) was added. After stirring at room temperature for 2 hours and then refluxing for 30 minutes, the resulting solution was acidified. The aqueous layer was extracted with ethyl acetate. The combined extracts were washed, dried and evaporated to leave the hydroxy ester as a gum. The residue was dissolved in ethanol (25 ml) and water (10 ml) was added. The homogenous mixture was refluxed, in the presence of 4-methylbenzenesulphonic acid monohydrate (100 mg), for 30 minutes. After cooling, the solvent was removed under reduced pressure to afford a gum. The crude product was purified by silica gel column chromatography to give the title compound as a brown oil (30 mg, 0.21 mmole, 4%); this product was homogeneous on TLC with the compound prepared above (A) and NMR and IR spectra were also identical.

methyl
4-(Benzoylamino)dihydro-2(3H)-furanone (183)

The general procedure (E) for *N*-benzoylation of ammonium salts was used. Thus the title compound was obtained as a light yellow solid (532 mg, 2.43 mmole, 61%);

m.p. 60-62°;

υ_{max} ($CHBr_3$) 3450 (NH), 1770 (lactone C=O), 1660 and 1530 cm^{-1} (amide C=O);

δ_{PMR} (60 MHz; $CDCl_3$) 2.35 to 2.65 (2H, m, $C\underline{H}_2CO$), 2.75 to 3.05 (1H, m, $C\underline{H}CH_2CO$), 3.5 (2H, t, *J* = 4 Hz, $NHC\underline{H}_2$), 3.95 to 4.4 (2H, m, $OC\underline{H}_2$), 7.2 to 7.6 and 7.65 to 7.95 (5H, m, aromatic protons) and 6.1 (1H, broad s, $N\underline{H}$),

δ_{PMR} (200 MHz; $CDCl_3$) 2.32 and 2.40 (1H, 2xd, *J* = 6 and 6 Hz, $\underline{H}CHCO$), 2.60 and 2.70 (1H, 2xd, *J* = 8 and 8 Hz, $C\underline{H}CO$), 2.82 to 3.04 (1H, m, $C\underline{H}CH_2CO$), 3.4-3.62(2H, dABq, J = 6 and 6 Hz; $NC\underline{H}_2$), 4.14 and 4.19 (1H, 2xd, *J* = 5 and 5 Hz, $O\underline{H}CH$), 4.38 and 4.42 (1H, 2xd, *J* = 7 and 7 Hz, $OHC\underline{H}$), 6.6 (1H, broad s, $N\underline{H}$), 7.3-7.54 and 7.64-7.80 (5H, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 32.16 ($\underline{C}HCH_2CO$), 35.67 ($\underline{C}H_2CO$), 41.73 ($N\underline{C}H_2$), 71.54 ($O\underline{C}H_2$), 127.40, 128.77, 131.90 and 134.30 (aromatic carbon atoms), 168.94 (benzoate $\underline{C}$=O) and 177.79 (lactone $\underline{C}$=O);

[Found: C, 64.9; H, 5.9; N, 6.8; $C_{12}H_{13}NO_3 \cdot 0.1H_2O$ (221.0) requires C, 65.1; H, 6.0; N, 6.4%];

TLC: Rf = 0.5 (solvent system H).

Ethyl 4-(benzoyloxy)-2-butenoate (187)

A mixture of ethyl 4-bromo-2-butenoate (2.77 g, 14.4 mmole) and benzoic acid (2.3 g, 18.8 mmole) in N,N-dimethyl formamide (17 ml) was stirred rapidly and anhydrous potassium carbonate (4.4 g, 31.8 mmole) was added. The mixture was stirred at room temperature for 1.5 hours. Then the reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated sodium hydrogen carbonate solution, water, dried and evaporated to leave a pale brown liquid (3.31 g, 14.2 mmole, 98%);

υ_{max} (film) 1710 (ester) and 1655 cm^{-1} (C=C);

δ_{PMR} (200 MHz; $CDCl_3$) 1.3 (3H, t, *J* =7.6 Hz, $OCH_2C\underline{H}_3$), 4.21 (2H, *q*, J = 7.6 Hz, $OC\underline{H}_2CH_3$), 4.98 (2H, dd, *J* = 2 and 4.5 Hz, $C\underline{H}_2C=$), 6.1 (1H, 2xt, *J* = 2 and 2 Hz, $CH_2C\underline{H}=$), 7.05 (1H, 2xt, *J* = 4.5 and 4.5 Hz, $=\underline{H}CCO$) and 7.3-7.62 and 8.0-8.1 (5H, m, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 14.25 ($OCH_2\underline{C}H_3$), 60.67 ($O\underline{C}H_2CH_3$), 63.15 ($O\underline{C}H_2C=$), 122.58 ($\underline{C}=CCO$), 128.7, 130.01 and 133.59 (aromatic carbon atoms), 141.59 ($C=\underline{C}CO$), and 166.01 (benzoate and ester $\underline{C}=O$);

[Found: C, 64.8; H, 5.8 ; $C_{13}H_{14}O_4 \cdot 0.4H_2O$ (241.4) requires C, 64.7; H, 6.1%];

TLC: Rf = 0.84 (solvent system J).

Ethyl 4-(benzoyloxy)-3-(nitromethyl)butanoate (188)

A mixture of ethyl 4-(benzoyloxy)-2-butenoate (500 mg, 2.14 mmole), nitromethane (2.2 ml), water (0.7 ml) and dichloromethane (7 ml) was stirred rapidly and treated with 40% aqueous tetrabutylammonium hydroxide solution, dropwise. Then the orange coloured reaction mixture was stirred at room temperature for one hour. This was partitioned between ethyl acetate and 1 N aqueous hydrochloric acid solution. After shaking, the organic layer was decolourized, which was then separated, washed, dried and evaporated to leave a brown oil. The crude product was purified by silica gel column chromatography, eluting with a mixture of ethyl acetate and petrol ether 40-60^{o} (1:4; 1:3 and 1:2). Fractions containing the required product were combined and evaporated to leave the title ester as a yellow oil (288 mg, 0.97 mmole, 45%);

υ_{max} (film) 1715 (ester), 1540 and 1370 cm^{-1} (NO_2);

δ_{PMR} (200 MHz; $CDCl_3$) 1.24 (3H, t, $\underline{J}$ = 7.6 Hz, $OCH_2C\underline{H}_3$), 2.58 (2H, dd, $\underline{J}$ = 2 and 7 Hz, $C\underline{H}_2CO$), 3.18 (1H, m, $C\underline{H}CH_2CO$), 4.18 (2H, q, $\underline{J}$ = 7.6 Hz, $OC\underline{H}_2CH_3$), 4.40 and 4.42 (2H, dd, $\underline{J}$ = 1 & 7 Hz, $NC\underline{H}_2CH$), 4.62 (2H, d, $\underline{J}$ = 7 Hz, $OC\underline{H}_2$), 7.39-7.62 and 7.95-8.1 (5H, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 14.12 ($OCH_2\underline{C}H_3$), 33.46 ($\underline{C}HCH_2CO$), 34.04 ($\underline{C}H_2CO$), 61.26 ($O\underline{C}H_2CH_3$), 64.45 ($O\underline{C}H_2CH$), 76.17 ($N\underline{C}H_2$), 128.77, 129.88 and 133.65 (aromatic carbon atoms), 166.33 (benzoate $\underline{C}$=O), 171.02 (ester $\underline{C}$=O);

[Found: C, 58.1; H, 5.8; N, 4.2 ; $C_{14}H_{17}NO_6$ (296.3) requires C, 56.9; H, 5.8; N, 4.7%];

TLC: Rf = 0.70 (solvent system J).

Diethyl 2-formylbutanedioate (192)

A mixture of diethyl butanedioate (10.0 g, 57.5 mmole) and ethyl formate (6.0 g, 81 mmole) in diethyl ether (80 ml) was stirred rapidly and 80% sodium hydride (1.9 g) was added, portionwise. Then the mixture was heated, slowly until reflux. After heating for 45 minutes, the yellow solution turned solid. The reaction was stopped and the reaction mixture was allowed to cool. Then the mixture was acidified with dilute sulphuric acid solution to pH 1. The organic layer was separated. The aqueous layer was extracted with more diethyl ether. The combined extract was washed, dried and evaporated and then distilled at 110-114^{o} (0.4 mm Hg) to leave the title compound as a yellow oil (6.98 g, 34.5 mmole, 61%);

υ_{max} (film) 3425 (OH), 1710 (ester) and 1630 cm^{-1} (C=C);

δ_{PMR} (60 MHz; $CDCl_3$) 1.3 (6H, 2xt, $\underline{J}$ = 7 Hz, 2 x $OCH_2C\underline{H}_3$), 3.02 (2H, d, $\underline{J}$ = 6 Hz, $C\underline{H}_2CH$), 3.2 (2H, s, $C\underline{H}_2$, enolic form), 3.65 (1H, t, $\underline{J}$ = 6 Hz, $CH_2C\underline{H}$), 4.3 (4H, 2xq, $\underline{J}$ = 7 Hz, 2 x $OC\underline{H}_2CH_3$);

δ_{CMR} (15 MHz; $CDCl_3$) 13.9 ($CH_2\underline{C}H_3$), 29.9 and 32.9 ($\underline{C}H_2CO$; both formyl and enolic form), 54.0 ($H\underset{\overset{\|}{O}}{C}\underline{C}H$), 60.6, 61.0 and 61.9 ($O\underline{C}H_2CH_3$), 99.4 and 104.5 ($\underline{C}=\underline{C}$), 162.8, 168.1 171.2, 171.6 and 171.8 ($\underline{C}$=O) and 195.9 ($H\underline{C}$=O);

G.C. at 150^{o}: Rt = 4.8 minutes; *procedure 2;*

TLC: Rf = 0.45 (solvent system S; stained reddish brown with alcoholic $FeCl_3$ solution).

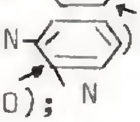
<u>Diethyl 2-[[(2,4-dinitrophenyl)hydrazono]methyl]butanedioate (193)</u>

A solution diethyl 2-formylbutanedioate (1.04 g, 5.15 mmole) in ethanol (16.5 ml) was stirred and 2,4-dinitrophenylhydrazine (0.98 g, 4.95 mmole) and acetic acid (0.5 ml) were added. The mixture was heated to reflux. After refluxing for 2.75 hours, the reaction was complete. The orange solid precipitated out on cooling was filtered. It was recrystallized from ethanol to give the <u>title hydrazone</u> as orange coloured crystals (1.34 g, 3.51 mmole, 70%);

m.p. 90-91^{o} (lit.[226] 89-91^{o});

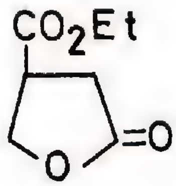
υ_{max} (Nujol) 3240 (NH), 1735 and 1708 (C=O), 1625 and 1590 cm^{-1} (C=N);

δ_{PMR} (100 MHz; $CDCl_3$ and DMSOd^6) 1.3 (6H, 2xt, $\underline{J}$ = 8 Hz, 2 x $OCH_2C\underline{H}_3$), 3.1 (2H, d, $\underline{J}$ = 7 Hz, $C\underline{H}_2CH$), 4.08 (1H, t, $\underline{J}$ = 7 Hz, $C\underline{H}CH_2$), 4.35 (4H, 2xq, $\underline{J}$ = 8 Hz, 2 x $C\underline{H}_2CH_3$), 8.3, 8.6 and 9.42 (3H, aromatic protons) and 12.18 (1H, NH);

δ_{CMR} (15 MHz; $CDCl_3$ and DMSOd^6) 14.1 ($CH_2\underline{C}H_3$), 33.2 ($\underline{C}H_2$), 44.7 ($CH_2\underline{C}H$), 60.9 and 61.7 (2 x $O\underline{C}H_2CH_3$), 116.8 (NH-), 123.3 (NH-), 129.9 (O_2N-), 138.2 (NH), 145.3 (HN-), 147.9 (HN-N and H$\underline{C}$=N), 170.3 and 171.2 ($\underline{C}$=O);

TLC: Rf = 0.75 (solvent system S).

Ethyl tetrahydro-5-oxo-3-furancarboxylate (194)



(194)

A solution of diethyl 2-formylbutanedioate (20.96 g, 104 mmole) in ethanol (200 ml) was stirred at room temperature and treated with sodium tetrahydridoborate (3.9 g, 103 mmole), in portions, over a period of 30 minutes. Then the cloudy mixture was stirred at 70° for 2.5 hours. The resulting mixture was allowed to stir at room temperature for 4 days. Then it was cooled in an ice-bath, quenched with ice (10 g) and then concentrated hydrochloric acid (12 ml) was slowly added, with vigorous stirring. The solvent was removed and the residue was dissolved in trichloromethane. The organic layer was separated, washed with saturated brine, dried and evaporated to leave a brown oil, which was distilled to give the title ester as an almost colourless liquid (1.84 g, 11.63 mmole, 11%);

b.p. 100-110° at 0.11 mm Hg (lit.[225f] b.p. 154° at 19 mm Hg);

υ_{max} (film) 2950 (C-H), 1765 (lactone) and 1715 cm^{-1} (ester);

δ_{PMR} (60 MHz, $CDCl_3$) 1.3 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 2.6-3.1 (2H, m, $C\underline{H}_2CO$), 3.4-3.6 (1H, m, $C\underline{H}CO$), 4.0-4.7 (4H, m, $OC\underline{H}_2CH_3$ and $C\underline{H}_2O$);

δ_{CMR} (15 MHz; $CDCl_3$) 14.1 ($CH_2\underline{C}H_3$), 30.9 ($\underline{C}HCH_2CO$), 40.1 ($\underline{C}HCO_2$), 62.0 ($O\underline{C}H_2CH_3$), 69.2 ($\underline{C}H_2O$), 171.5 ($\underline{C}O_2Et$) and 176.4 ($\underline{C}$=O, lactone);

G.C. at 120°: Rt = 3.5 minutes; procedure 2;

TLC: Rf = 0.45 (solvent system S).

4-Bromo-3-(bromomethyl)-2-butenoic acid (199)

The procedure reported by Boeckman[230] for the bromination of 3-methyl-2-butenoic acid was followed. Thus the title acid was obtained as a golden yellow syrup (38.19 g, 0.15 mole, 100%);

υ_{max} (film) 3500 to 2400 (OH), 1695 (C=O) and 1635 cm^{-1} (C=C);

δ_{PMR} (60 MHz; $CDCl_3$) 1.18 (1H, s, O$\underline{H}$), 4.19 (2H, s, $BrC\underline{H}_2$), 4.73 (2H, s, $BrC\underline{H}_2$) and 6.06 (1H, s, =$C\underline{H}CO$);

δ_{CMR} (15 MHz; $CDCl_3$) 25.13 ($Br\underline{C}H_2$), 33.33 ($Br\underline{C}H_2$), 120.96 (=$\underline{C}HCO$), 153.05 ($\underline{C}$=CHCO) and 170.24 ($\underline{C}$=O);

TLC: Rf = o.75 (solvent system H) and Rf = 0.65 (solvent system D).

4-(Bromomethyl)-2(5H)-furanone (200)

The title lactone was prepared from compound (199) according to the method described by Boeckman.[230] Thus the product was isolated as reddish brown oil (21.36 g, 0.12 mole, 83%);

υ_{max} (film) 1765 and 1730 cm^{-1} ($\Delta^{\alpha,\beta}$-butenolide);

δ_{PMR} (200 MHz; $CDCl_3$) 4.23 (2H, dt, J = 1 Hz, $BrC\underline{H}_2$), 4.97 (2H, dt, J = 1 Hz, $OC\underline{H}_2$) and 6.18 (1H, dt, J = 1 and 1 Hz, =$C\underline{H}CO$);

δ_{CMR} (15 MHz; $CDCl_3$) 22.85 ($Br\underline{C}H_2$), 72.13 ($O\underline{C}H_2$), 118.88 (=$\underline{C}$HCO), 164.19 ($\underline{C}$=CHCO) and 173.10 ($\underline{C}$=O);

TLC: Rf = 0.55 (solvent system J).

4-(Benzoyloxy)-2(5H)-furanone (201)

To a mixture of 4-(bromomethyl)-2(5H)-furanone (1.45 g, 8.2 mmole) and benzoic acid (1.0 g, 8.2 mmole) in N,N-dimethylformamide (10 ml) was added anhydrous potassium carbonate (1.34 g). After stirring at room temperature for one hour, the dark brown reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was separated, dried and evaporated to afford the title compound as a white solid (1.45 g, 6.6 mmole, 78%);

m.p. 105-109^{o} (from EtOAc);

υ_{max} (film) 1785 and 1740 ($\Delta^{\alpha,\beta}$-butenolide) and 1715 cm^{-1} (benzoate);

δ_{PMR} (200 MHz; $CDCl_3$) 4.95 (2H, dt, $\underline{J}$ = 2 Hz, $OC\underline{H}_2$), 5.23 (2H, dt, $\underline{J}$ = 1 Hz $Ph\overset{O}{\overset{\|}{C}}OC\underline{H}_2$), 6.18 (1H, dt, $\underline{J}$ = 1 and 2 Hz, =C$\underline{H}$CO), 7.41-7.7 and 8.0-8.12 (5H, m, aromatic protons);

δ_{CMR} (15MHz; $CDCl_3$) 59.89 ($PhCO_2\underline{C}H_2$), 71.28 ($O\underline{C}H_2$), 117.44 (=$\underline{C}$HCO), 128.9, 129.94 and 134.04 (aromatic carbon atoms), 163.73 ($\underline{C}$=CHCO), 166.01 (benzoate $\underline{C}$=O) and 172.91 (lactone $\underline{C}$=O);

[Found: C, 65.1; H, 4.6; $C_{12}H_{10}O_4$. $0.1H_2O$ (220.0) requires C, 65.5; H, 5.1%];

TLC: Rf = 0.4 (solvent system J).

4-(Azidomethyl)-2(5H)-furanone (202)

The general procedure [(D), conditions (ii)] for azide displacement on the bromide (200) was used. Thus the title azide was obtained as a brown oil (2.83 g, 20.28 mmole, 75%);

υ_{max} 2100 (N_3), 1775 and 1740 cm^{-1} ($\Delta^{\alpha,\beta}$-butenolide);

δ_{PMR} (200 MHz; $CDCl_3$) 4.32 (2H, dt, J = 1 Hz NCH_2), 4.83 (2H, dt, J = 1.7 Hz, OCH_2) and 6.1 (1H, dt, J = 1 and 1.7 Hz, =CHCO);

δ_{CMR} (15 MHz; $CDCl_3$) 48.17 (NCH_2), 71.54 (OCH_2), 117.77 (=CHCO), 163.3 (C=CHCO) and 172.97 (C=O);

[Found: C, 43.4; H, 3.9; N, 25.5; $C_5H_5N_3O_2$ (139.1) requires C, 43.2; H, 3.6; N, 30.2%];

Mass spectrum: M/Z 139 (M^+), $C_5H_5N_3O_2$ requires 139.11;

TLC: Rf = 0.4 (solvent system J).

2-[(2,5-Dihydro-5-oxo-3-furanyl)methyl]-1H-isoindole-1,3(2H)-dione (203)

A mixture of 4-(bromomethyl)-2(5H)-furanone (1.0 g, 5.66 mmole) and 1H-isoindole-1,3(2H)-dione potassium salt (1.05 g, 5.66 mmole) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 50 minutes. Then the reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed, dried and evaporated to leave a slurry of solid. The solid was further purified by column chromatography, eluting with a mixture of petrol ether 40-60^o and ethyl acetate (2:1). Fractions containing the required product were combined and evaporated to leave the title compound as a light

yellow solid (613 mg, 2.52 mmole, 45%);

m.p. 217-218^{o};

υ_{max} ($CHBr_3$) 1780 and 1730 ($\Delta^{\alpha,\beta}$-butenolide) and 1720 cm^{-1} (amide);

δ_{PMR} (200 MHz; acetone-d^6) 4.50 (2H, dt, $\underline{J}$ = 1 Hz, $NC\underline{H}_2$), 4.98 (2H, dt, $\underline{J}$ = 1.6 Hz, $OC\underline{H}_2$), 6.19 (1H, dt, $\underline{J}$ = 1 and 1.6 Hz, =C$\underline{H}$CO), 7.85 (4H, s, aromatic protons);

δ_{CMR} (15 MHz; acetone-d^6) 23.89 ($N\underline{C}H_2$), 72.46 ($O\underline{C}H_2$), 119.01 (=$\underline{C}$HCO), 123.82 and 134.95 (aromatic carbon atoms), 165.81 ($\underline{C}$=CHCO), 169.81 (amide $\underline{C}$=O) and 174.61 (lactone $\underline{C}$=O);

[Found: C, 62.7; H, 3.4; N, 8.8 ; $C_{13}H_9NO_4$. 0.2DMF (254.6) requires C, 64.1; H, 4.1; N, 6.6%];

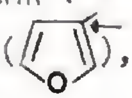
TLC: Rf = 0.5 (solvent system J).

<u>3-(Chloromethyl)furan (215)</u>

The <u>title compound</u> was prepared from the alcohol (213) according to a literature procedure,[239] as a light brown oil (3.66 g, 31.4 mmole, 62%);

υ_{max} (film) 1595 and 1500 cm^{-1} (C=C);

δ_{PMR} (200 MHz; $CDCl_3$) 4.50 (2H, s, $ClC\underline{H}_2$), 6.41 (1H, m, C-2$\underline{H}$ proton), and 7.3-7.45 (2H, m, C-4$\underline{H}$ and 5$\underline{H}$ protons);

δ_{CMR} (15 MHz; $CDCl_3$) 37.17 ($\underline{C}H_2Cl$), 110.60 (), 122.71 (), and 141.01 and 144.14 (2 x furan carbon atoms);

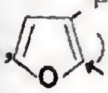
TLC: Rf = 0.9 (solvent system R).

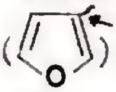
<u>2-[(3-furanyl)methyl]-1H-isoindole-1,3(2H)-dione (216)</u>

3-(Chloromethyl)furan (3.50 g, 30.03 mmole) was dissolved in N,N-dimethylformamide (35 ml). The mixture was stirred in a water-bath and treated with 1H-isoindole-1,3(2H)-dione potassium salt (5.56 g, 30.03 mmole), in portions, over 5 minutes. (An exothermic reaction occurred). After the addition, the reaction mixture was stirred at room temperature for 2 days. Then it was diluted with ethyl acetate and washed with water, dried and evaporated to leave a brown solid. The crude product was purified by column chromatography to give the <u>title compound</u> as a yellow crystalline residue, which turned darker in colour on storage (2.82 g, 12.44 mmole, 41%);

m.p. 74-76^{o};

υ_{max} (Nujol) 1695 (amide), 1600 and 1590 cm^{-1} (C=C);

δ_{PMR} (200 MHz; $CDCl_3$) 4.70 (2H, s, $C\underline{H}_2N$), 6.45 (1H, m, ), 7.32 and 7.52 (2H, m, ) and 7.62-7.78 and 7.79-7.90 (4H, m, );

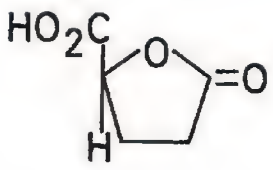
δ_{CMR} (15 MHz; $CDCl_3$) 31.96 ($\underline{C}H_2N$), 110.86 (), 120.37 (phthamido carbon atoms), 123.23 (), 132.09 and 133.98 (phthalamido carbon atoms), 141.33 and 143.22 (2 x furan carbon atoms) and 167.83 ($\underline{C}$=O);

[Found: C, 68.2; H, 4.1; N, 5.8; $C_{13}H_9NO_3 \cdot 0.1H_2O$ (229.0) requires C, 68.3; H, 4.2; N, 6.1%];

TLC: Rf = 0.85 (solvent system J).

Preparations leading to γ-aminomethyl-γ-butyrolactone salts (232) and (252)

(S)-tetrahydro-5-oxo-2-furancarboxylic acid (225)



(225)

The preparation of the title compound from L-glutamic acid (224) was carried out according to the method described by Koga et al.[242d] The reaction afforded the title acid as a light yellow syrup (16.2 g, 0.12 mmole, 100%);

υ_{max} (film) 3600 to 2200 (OH), 1780 (lactone) and 1715 cm^{-1} (C=O);

δ_{PMR} (60 MHz; $CDCl_3$) 2.1-3.0 (4H, m, $C\underline{H}_2C\underline{H}_2CO$) and 5.1 (1H, m, $C\underline{H}$);

δ_{CMR} (15 MHz; D_2O and dioxane) 29.2 ($\underline{C}H_2CH_2CO$), 30.0 ($\underline{C}H_2CO$), 69.9 ($\underline{C}H$), 178.3 ($\underline{C}O_2H$) and 178.5 (lactone);

TLC: Rf = 0.5 (solvent system H, under UV, but became a streaky trace when developed in iodine vapour).

N.B. A second compound (ca. 20%) is present as indicated by CMR spectroscopy (presumably the open-chain α-hydroxyglutaric acid).

Ethyl (S)-tetrahydro-5-oxo-2-furancarboxylate (226)

(A) By esterification of the lactonic acid (225)

The method reported by Koga et al[242d] was used. Thus the title ester was obtained as a light yellow oil (3.2 g, 20.0 mmole, 17%);

b.p 104-106^o at 0.7 mm Hg [lit.[242d] b.p. 135-140^o (10 mm)];

$[\alpha]_D$ + 10.2^o (C=0.46; EtOH) [lit.[242d] $[\alpha]_D^{32}$ +11.5 (C=2.93; EtOH)];

υ_{max} (film) 1785 (lactone) and 1730 cm^{-1} (ester);

δ_{PMR} (60 MHz; $CDCl_3$) 1.32 (3H, t, $\underline{J}$ = 8 Hz, $CH_2C\underline{H}_3$), 2.0-2.9 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 4.4 (2H, q, $\underline{J}$ = 8 Hz, $C\underline{H}_2CH_3$) and 4.9-5.15 (1H, m, C$\underline{H}$);

δ_{CMR} (15 MHz; $CDCl_3$) 14.1 ($\underline{C}H_3$), 25.9 ($\underline{C}H_2CH_2CO$), 26.8 ($\underline{C}H_2CO$), 62.1 ($CH_3\underline{C}H_2O$), 75.9 ($\underline{C}H$), 170.3 (ester $\underline{C}$=O) and 176.4 (lactone $\underline{C}$=O);

G.C. at 100^o: Rt = 3.3 minutes; procedure 2;

TLC: Rf = 0.8 (solvent system H).

N.B. The product still contained ca. 10% of the open-chain hydroxy ester, see later.

(B) Treating the hydroxy ester (227) with TFA

Diethyl (S)-2-hydroxypentanedioate (100 mg, 0.47 mmole) was dissolved in trifluoroacetic acid (1 ml). After standing at room temperature for 15 minutes, the solvent was

removed under reduced pressure and then dried over phosphorus pentoxide and sodium hydroxide to give the title ester as a yellow oil (74 mg, 0.47 mmole, 100%); both IR and NMR spectra were identical with the ester prepared above; TLC indicated about 10% of the hydroxy ester was still present.

Diethyl (S)-2-hydroxypentanedioate (227)

Benzene (30 ml) and 4-methylbenzenesulphonic acid monohydrate (200 mg) was added to a solution of 5-oxo-tetrahydrofuran-2-carboxylic acid (7.62 g, 60 mmole) in ethanol (13 ml). The mixture was refluxed for 2.5 hours. Then it was allowed to stand at room temperature for 2 days. The reaction mixture was diluted with benzene, washed with water, saturated sodium hydrogen carbonate solution and then brine. The organic layer was separated, dried and evaporated to leave the title hydroxy ester as a yellow oil (7.83 g, 38.9 mmole, 68%);

υ_{max} (film) 3450 (OH) and 1715 cm^{-1} (ester);

δ_{PMR} (60 MHz; $CDCl_3$) 1.3 (6H, 2t, J = 7 Hz, 2 x $CH_2C\underline{H}_3$), 1.6-2.6 (5H, m, $C\underline{H}C\underline{H}_2C\underline{H}_2CO$), 3.9 (1H, broad singlet, $O\underline{H}$) and 4.25 (4H, 2q, J = 7 Hz, 2 x $C\underline{H}_2CH_3$);

δ_{CMR} (15 MHz; $CDCl_3$) 14.1 ($\underline{C}H_3$), 29.4 ($\underline{C}H_2CH_2CO$), 29.8 ($\underline{C}H_2CO$), 60.6 ($\underline{C}H_2CH_3$), 61.9 ($\underline{C}H_2CH_3$), 69.6 ($H\underline{C}$-OH), 173.5 ($\underline{C}$=O) and 175.0 ($\underline{C}$=O);

G.C. at 100^o: Rt = 5.2 minutes; procedure 2;

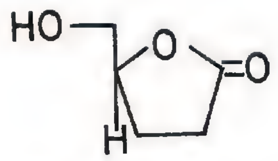
TLC: 0.75 (solvent system H).

[Found: C, 51.1; H, 6.9 ; $C_9H_{15}O_5$. $0.5H_2O$ (212.2)

requires C, 51.0; H, 7.5).

N.B. TLC and NMR indicated about 10% of the lactone was present.

<u>(S)-Dihydro-5-(hydroxymethyl)-2(3H)-furanone (228)</u>



(228)

The <u>title hydroxy compound</u> was prepared from the ester (226) according to a literature method reported by Koga <u>et al</u>.[242d] The product was a light yellow oil (370 mg, 3.2 mmole, 51%); $[\alpha]_D$ + 32° (C=0.5; EtOH) [lit.[242d] $[\alpha]_D^{26}$ + 31.3 (C=2.92; EtOH)];

ν_{max} (film) 3420 (OH), 2940 (C-H) and 1765 cm^{-1} (lactone);

δ_{PMR} (100 MHz; $CDCl_3$) 0.96-1.4 (2H, m, $C\underline{H}_2CH_2CO$), 1.4-1.7 (2H, m, $C\underline{H}_2CO$), 3.0 (1H, broad singlet, $O\underline{H}$), 3.4-4.2 (2H, m, $HOC\underline{H}_2$) and 4.4-4.7 (1H, m, $C\underline{H}O$);

δ_{CMR} (15 MHz; $CDCl_3$), 23.1 ($\underline{C}H_2CH_2CO$), 28.7 ($\underline{C}H_2CO$), 64.1 ($HO\underline{C}H_2$), 81.1 ($\underline{C}HO$) and 178.3 (lactone $\underline{C}$=O);

TLC: Rf = 0.4 (solvent system C).

(S)-5-[(Benzoyloxy)methyl]dihydro-2(3H)-furanone (229)

The general procedure (F) for O-benzoylation of hydroxy compounds was used. Thus (S)-dihydro-5-(hydroxymethyl)-2(3H)-furanone was reacted with benzoyl chloride, in the presence of triethylamine, to give the title benzoate as a light yellow oil (532 mg, 2.42 mmole, 56%); $[\alpha]_D = + 37.8^o$ (C=0.5; EtOH) [lit.[242d] $[\alpha]_D^{26}$ + 48.2^o (C=1.03)];

υ_{max} (film) 2950 (C-H), 1780 (lactone) and 1720 cm^{-1} (benzoate);

δ_{PMR} (100 MHz; $CDCl_3$) 1.9-2.4(2H, m, $C\underline{H}_2CH_2CO$), 2.3-2.8 (2H, m, $C\underline{H}_2CO$), 4.0-4.65 (2H, m, $-OC\underline{H}_2$), 4.7-4.98 (1H, m, $H\underline{C}$-O), 7.2-7.6 and 7.9-8.1 (aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 24.0 ($\underline{C}H_2CH_2CO$), 28.2 ($\underline{C}H_2CO$), 65.8 ($-O\underline{C}H_2$), 77.5 ($H\underline{C}O$), 128.7 and 129.9 (5 unsubstituted aromatic carbons), 133.6 (CO), 166.4 (Ph-$\underline{C}$=O) and 176.8 (lactone $\underline{C}$=O);

[Found: C, 64.4; H, 5.7; $C_{12}H_{12}O_4 \cdot 0.2H_2O$ (223.8) requires C, 64.4; H, 5.6%]

TLC: Rf = 0.7 (solvent system N).

(S)-Dihydro-5-[[[(4-methylphenyl)sulphonyl]oxy]methyl]-2(3H)-furanone (230)

The general procedure [(L), conditions (i)] for O-sulphonylation of alcohols was used. Thus (S)-dihydro-5-(hydroxymethyl)-2(3H)-furanone was reacted with 4-methylbenzenesulphonyl chloride, in the presence of triethylamine, to give the title tosylate as a colourless crystalline residue (0.4 g, 2.1 mmole, 49%);

m.p. 88^{o} (lit.[242c] m.p. 87^{o});

$[\alpha]_D = + 44.6^{o}$ (C = 0.61; $CHCl_3$)[lit.[242c] $[\alpha]_D$ + 44.5^{o} (C=0.95, $CHCl_3$)];

υ_{max} (film) 2950 (C-H), 1780 (lactone), 1350 and 1160 cm^{-1} (SO_2);

δ_{PMR} (100 MHz ; $CDCl_3$) 0.8-1.5 (2H, m, $C\underline{H}_2CH_2CO$), 1.4-1.8 (2H, m, $C\underline{H}_2CO$), 2.42 (3H, s, $ArC\underline{H}_3$), 4.0-4.35 (2H, m, $OC\underline{H}_2$), 4.38-4.9 (1H, m, $\underline{H}CO$), 7.35 (2H, d, $\underline{J}$ = 8 Hz, aromatic protons) and 7.78 (2H, d, $\underline{J}$ = 8 Hz, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 21.7 ($Ar\underline{C}H_3$), 23.5 ($\underline{C}H_2CH_2CO$), 27.9 ($\underline{C}H_2CO$), 70.1 ($O\underline{C}H_2$), 76.6 ($H\underline{C}O$), 128.2 (CH_3-), 130.2 (CH_3-), 132.4 (CH_3-), 145.7 (-S) and 176.4 ($\underline{C}$=O);

[Found: C, 51.9; H, 5.4; $C_{12}H_{14}O_5S$ (279.3) requires C, 51.6; H, 5.4%];

TLC: Rf = 0.65 (solvent system N).

<u>(S)-5-(Azidomethyl)dihydro-2(3H)-furanone (231)</u>

The <u>title azide</u> was prepared by using the general procedure [(D), conditions (i)] for azide displacement on the tosylate (230). Thus product was isolated as a brown oil (225 mg, 1.6 mmole, 87%);

$[\alpha]_D = + 85.7^{o}$ (C=0.7; $CHCl_3$) [lit.[246c] $[\alpha]_D = + 56^{o}$ (C=2; $CHCl_3$)];

υ_{max} (film) 2100 (N_3) and 1775 cm^{-1} (lactone);

δ_{PMR} (60 MHz; $CDCl_3$) 0.75-3.0 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 3.25-3.85 (2H, m, $N_3C\underline{H}_2$) and 4.5-4.9 (1H, m, $\underline{H}CO$);

δ_{CMR} (15 MHz; $CDCl_3$) 24.6 ($\underline{C}H_2CH_2CO$), 28.2 ($\underline{C}H_2CO$), 54.2 ($N_3\underline{C}H_2$), 78.1 ($H\underline{C}O$) and 176.6 ($\underline{C}$=O);

[Found: C, 42.0; H, 5.4; N, 29.7; $C_5H_7N_3O_2$ (141.3) requires C, 42.5; H, 5.0; N, 29.8%];

G.C. at 120^o: Rt = 2.8 minutes; procedure 2;

TLC: Rf = 0.6 (solvent system N).

<u>(S)-5-(Aminomethyl)dihydro-2(3H)-furanone hydrochloride (232)</u>

The product was obtained by the hydrogenation [general procedure (J)] of (S)-5-(azidomethyl)dihydro-2(3H)-furanone (1.42 g, 10.05 mmole) in the presence of 2 N hydrochloric acid. The <u>title hydrochloride</u> was isolated as a pale yellow hygroscopic solid (1.21 g, 8.04 mmole, 80%);

υ_{max} (Nujol) 3700 to 2200 ($\overset{+}{N}H_3$ and OH), and 1775 cm^{-1} (lactone);

δ_{PMR} (60 MHz; D_2O) 0.9-3.1 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 3.15-3.5 (2H, m, $C\underline{H}_2NH_2$), and 4.8-5.15 (1H, m, $\underline{H}CO$);

δ_{CMR} (15 MHz; D_2O and DSS as standard) 27.1 ($\underline{C}H_2CH_2CO$), 30.8 ($\underline{C}H_2CO$), 45.5 ($\underline{C}H_2NH_2$), 80.6 ($H\underline{C}O$) and 185.7 ($\underline{C}$=O);

[Found: C, 38.7; H, 6.5; N, 8.0; $C_5H_{10}ClNO_2 \cdot 0.5H_2O$ (160.6) requires C, 37.4; H, 6.8; N, 8.7%];

TLC: Rf = 0 (solvent system H).

N.B. A second (minor) set of signals were detected on ^{13}C-NMR, which was believed to be the ring-open form, with peaks at δ 31.31, 32.4, 47.14, 60.2 and 189.12.

(S)-5-[(Benzoylamino)methyl] dihydro-2(3H)-furanone (233)

The general procedure (E) for N-benzoylation of ammonium salts was used. Thus the treatment of (S)-5-(aminomethyl)-dihydro-2(3H)-furanone (150 mg, 1.0 mmole) with benzoyl chloride, in the presence of triethylamine, gave the title amide as a pale yellow gum (193 mg, 0.88 mmole, 89%);

υ_{max} (film) 3350 (NH), 1770 (lactone C=O), 1645 and 1540 cm^{-1} (CONH);

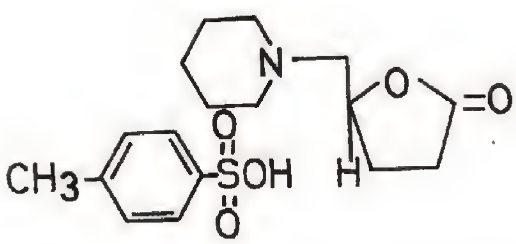
δ_{PMR} (60 MHz; $CDCl_3$) 0.75-2.8 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 3.25-4.2 (2H, m, $C\underline{H}_2N$), 4.5-5.0 (1H, m, $\underline{H}CO$), 6.95—7.3 (1H, bs, $N\underline{H}$), 7.3-7.65 and 7.65-8.1 (5H, m, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 24.86 ($\underline{C}H_2CH_2CO$), 28.58 ($\underline{C}H_2CO$), 43.42 ($\underline{C}H_2NH$), 79.75 ($H\underline{C}O$), 127.27, 128.83 and 132.09 (5x unsubstituted aromatic carbon atoms), 133.98 (1 substituted aromatic carbon atom), 168.29 ($\underline{C}ONH$) and 177.21 (lactone $\underline{C}$=O);

[Found: C, 65.0; H, 6.2; N, 5.7; $C_{12}H_{13}N$. $0.2H_2O$ (222.8) requires C, 64.7; H, 6.1; N, 6.3%];

TLC: Rf = 0.45 (solvent system H).

(S)-1-[(Tetrahydro-5-oxo-2-furanyl)methyl]piperidinium 4-methylbenesulphonic acid salt (246a)

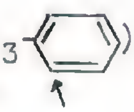


(246a)

A mixture of (S)-dihydro-5-[[[(4-methylphenyl) sulphonyl]oxy]methyl]-2(3H)-furanone (2.96 g, 10.99 mmole) and piperidine (0.935 g, 10.99 mmole) in ethanol (59 ml) was refluxed for 5 hours. Then the solvent was removed under reduced pressure to leave the <u>title salt</u> as a light brown gum (3.89 g, 10.90 mmole, 98%);

υ_{max} 3700 to 2300 ($\overset{+}{N}H$ and OH), 1770 (lactone), 1350 and 1160 cm^{-1} (SO_2);

δ_{PMR} (60 MHz; $CDCl_3$) 1.01-2.0 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 1.6-2.2 (6H, m, 3', 4' and 5' methylene protons of piperidine ring), 2.4 (3H, s, $ArC\underline{H}_3$), 2.2-3.85 (4H, m, 2' and 6' methylene protons of piperidine ring), 2.9-3.2 (2H, m, $NC\underline{H}_2$) and 4.45-4.95 (1H, m, $\underline{H}CO$);

δ_{CMR} (15 MHz; $CDCl_3$) 21.28 ($Ar\underline{C}H_3$), 22.39 (N-), 23.24 ($\underline{C}H_2CH_2CO$), 24.93 (N-), 28.25 ($\underline{C}H_2CO$), 44.79 (N-), 54.94 ($N\underline{C}H_2$), 78.19 ($H\underline{C}O$), 125.06 (CH_3-), 128.18 (CH_3-), 139.58 (CH_3-), 141.20 (-S) and 176.22 ($\underline{C}$=O);

TLC: Rf = 0 (solvent system H).

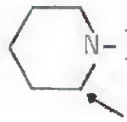
<u>(S)-1-[(Tetrahydro-5-oxo-2-furanyl)methyl]piperidinium hydrochloride (246b)</u>

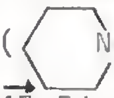
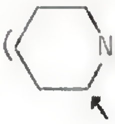
A mixture of (S)-dihydro-5-[[[(4-methylphenyl)-sulphonyl]oxy] methyl]-2(3H)-furanone (200 mg, 0.74 mmole) and piperidine (63 mg, 0.74 mmole) in ethanol (4 ml) was refluxed for 5 hours. Then the solvent was removed to leave a brown gum. The residue was dissolved in a small amount of water and put onto an Amberlite IRA 410 (Cl^-) column (20 g), eluting with water, at such a rate that a drop was formed

per 2 seconds. Fractions containing the required product were combined and evaporated to a gummy solid. This crude product was further purified by heating an aqueous solution of the hydrochloride with charcoal for 15 min at 70°. Then the suspension was filtered. The filtrate was evaporated to leave the <u>title hydrochloride</u> as a colourless crystalline residue (96 mg, 0.44 mmole, 60%);

υ_{max} (Nujol) 3700 to 2100 ($\overset{+}{N}H$ and OH) and 1770 cm^{-1} (lactone);

δ_{PMR} ($CDCl_3$) 1.2-2.0 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 1.5-2.2 (6H, m, 3', 4' and 5' methylene protons of piperidine ring), 2.0-3.2 (4H, m, 2' and 6' methylene protons of piperidine ring), 2.9-3.4 (2H, m, $NC\underline{H}_2$) and 4.4-5.0 (1H, m, $\underline{H}CO$);

δ_{CMR} (15 MHz; $CDCl_3$) 22.46 ( N-), 23.31 ($\underline{C}H_2CH_2CO$), 26.76 ( N-), 28.06 ($\underline{C}H_2CO$), 44.59 ( N-), 54.29 ($N\underline{C}H_2$), 81.05 ($H\underline{C}O$), 176.49 (C=O);

δ_{CMR} (D_2O and dioxane, reference to absolute zero) 59.83 ( N-), 60.54 ($\underline{C}H_2CH_2CO$), 63.34 ( N-), 66.14 ($\underline{C}H_2CO$), 82.94 ( N-), 91.33 ($N\underline{C}H_2$), 113.54 ($H\underline{C}O$) and 219.19 ($\underline{C}$=O);

[Found: C, 40.8; H, 8.0; N, 5.5; $C_{10}H_{18}ClNO_2 \cdot 4H_2O$ (292) requires C, 41.0; H, 8.9; N, 4.9%];

TLC: Rf = 0 (solvent system H).

N.B. The solid was very hygroscopic. Minor signals were also detected by C-13 NMR spectroscopy.

Dihydro-5-(iodomethyl)-2(3H)-furanone (249)

The procedure for iodolactonization of pent-4-enoic acid (248) reported by van Tamelen[248] was adopted. Thus the title iodide was isolated as a light brown oil (1.26g, 5.4 mmole, 100%);

υ_{max} (film) 1750 cm^{-1} (lactone).

δ_{PMR} (200 MHz; $CDCl_3$) 1.8-2.1 (1H, m, $\underline{H}CHCH_2CO$), 2.38-2.78 (3H, m, $C\underline{H}C\underline{H}_2CO$), 3.3 (1H, 2d, $\underline{J}$ 7.6 and 7.6 Hz, $IC\underline{H}$), 3.4 (1H, 2d, $\underline{J}$ 4.5 and 4.5 Hz, $IC\underline{H}$) and 4.42-4.62 (1H, m, $\underline{H}CO$),

δ_{CMR} (15 MHz; $CDCl_3$) 7.48 ($I\underline{C}H_2$), 28.12 ($\underline{C}H_2CH_2CO$), 28.84 ($\underline{C}H_2CO$), 78.58 ($H\underline{C}O$) and 176.48 ($\underline{C}$=O);

TLC: Rf = 0.54 (solvent system J).

5-(Benzoyloxy)dihydro-2(3H)-furanone (250)

A mixture of dihydro-5-(iodomethyl)-2(3H)-furanone (0.65 g, 5.29 mmole), benzoic acid (0.65 g, 5.3 mmole), 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) (1.4 g, 5.29 mmole) and potassium carbonate (1.37 g) in dichloromethane (20 ml) was stirred at room temperature for 2 days and then refluxed for 8 hours. By then, TLC indicated that the reaction was complete. Thus the reaction mixture was diluted with ethyl acetate, washed with water, saturated sodium hydrogen carbonate, and brine. The organic layer was separated, dried and evaporated to leave a brown oil. The crude product was purified on a silica gel column, eluting with a mixture of petrol ether 40-60^{o} and ethyl acetate (2:1). Fractions con-

taining the required product were combined and evaporated to leave the title compound as a light brown oil (395 mg, 1.64 mmole, 31%);

υ_{max} (film) 1775 (lactone C=O) and 1720 cm^{-1} (ester C=O);

δ_{PMR} (60 MHz; $CDCl_3$) 2.0-2.8 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 4.35-4.55 (2H, m, $OC\underline{H}_2$), 4.65-5.0 (1H, m, $\underline{H}CO$), 7.2-7.7 and 7.9-8.2 (5H, m, aromatic protons),

δ_{PMR} (200 MHz; $CDCl_3$) 2.02-2.22 (1H, m, $\underline{H}CHCH_2CO$), 2.3-2.59 (1H, m, $C\underline{H}CH_2CO$), 2.58-2.9 (2H, m, $C\underline{H}_2CO$), 4.42 (1H, 2d, $\underline{J}$ 2.8 and 2.5 Hz, $OC\underline{H}$), 4.58 (1H, 2d, $\underline{J}$ 1.8 and 1.8 Hz, $OC\underline{H}$), 4.8-4.98 (1H, m, $\underline{H}CO$), 7.38-7.42 and 7.95-8.1 (5H, m, aromatic protons);

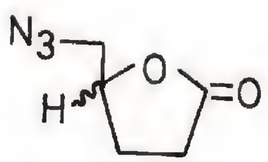
δ_{CMR} (50 MHz; $CDCl_3$) 23.97 ($\underline{C}H_2CH_2CO$), 28.17 ($\underline{C}H_2CO$), 65.72 ($O\underline{C}H_2$), 77.46 ($H\underline{C}O$), 128.53, 129.44 129.67 and 133.38 (6 aromatic carbon atoms), 166.09 (ester $\underline{C}$=O) and 176.54 (lactone $\underline{C}$=O);

[Found: C, 64.2; H, 5.4; $C_{12}H_{12}O_4$. $0.15H_2O$ (222.9) requires C, 64.6; H, 5.5%];

TLC: Rf = 0.55 (solvent system J).

<u>5-(Azidomethyl)dihydro-2(3H)-furanoen (251)</u>

(A) <u>From the iodide (249)</u>



(251)

The general procedure [(D), conditions (i)] for azide displacement was used. Thus the <u>title azide</u> was obtained from dihydro-5-(iodomethyl)-2(3H)-furanone (9.33 g, 40.8 mmole) as a brown liquid (3.18 g, 22.6 mmole, 56%);

ν_{max} (film) 2100 (N_3) and 1770 cm^{-1} (lactone);

δ_{PMR} (60 MHz; $CDCl_3$) 1.6 to 2.9 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 3.4 to 3.7 (2H, m, $NC\underline{H}_2$) and 4.4 to 4.75 (1H, m, $\underline{H}CO$);

δ_{PMR} (200 Mhz; $CDCl_3$) 1.98-2.18 (1H, m, $\underline{H}CHCH_2CO$), 2.20-2.5 (1H, m, $C\underline{H}CH_2CO$), 2.5-2.7 (2H, m, $C\underline{H}_2CO$), 3.43 (1H, 2d, $\underline{J}$ 2.5 and 2.2 Hz, $NC\underline{H}$), 3.62 (1H, 2d, $\underline{J}$ 2.5 and 2.2 Hz, $NC\underline{H}$), 3.62 (1H, 2d, $\underline{J}$ 2 and 2 Hz, $NC\underline{H}$) and 4.5-4.75 (1H, m, $\underline{H}CO$);

δ_{CMR} (15 MHz; $CDCl_3$) 24.60 ($\underline{C}H_2CH_2CO$), 28.25 ($\underline{C}H_2CO$), 54.23 ($N\underline{C}H_2$), 78.25 ($H\underline{C}O$) and 176.75 ($\underline{C}=O$);

Mass spectrum: M/Z 141 (M^+);

[Found: C, 42.6; H, 5.1; N, 29.0; $C_5H_7N_3O_2$ (141.1) requires C, 42.6; H, 5.0; N, 29.8%];

TLC: Rf = 0.54 (solvent system N).

(B) <u>From the lactonic ester (259)</u>

Ethyl 5-(azidomethyl)-tetrahydro-2-oxo-3-furancarboxylate (4.5 g, 21.2 mmole) was dissolved in tetrafuran (2 ml) and 6 N aqueous hydrochloric acid solution (45 ml) was added amd refluxed for one hour. After cooling, the solvent was removed under reduced pressure to leave a brown oil. The crude product was purified by silica gel column chromatography, eluting with a mixture of petrol ether 40-60^o and ethyl acetate (1:1) and then ethyl acetate.

Fractions containing the required product were combined and evaporated to leave the title compound as a light brown oil (1.2 g, 8.3 mmole, 39%);

IR & NMR spectra and TLC of this compound were identical with those measured for the compound prepared previously, procedure A.

5-(Aminomethyl)dihydro-2(3H)-furanone, hydrochloride (252)

(A) Via reduction of the azide (251)

The title salt was prepared by hydrogenolysis of 5-(azidomethyl)dihydro-2(3H)-furanone (2.0 g, 14.2 mmole), in the presence of aqueous hydrochloric acid, using the general procedure (J). It was isolated as a waxy yellow solid, a dihydrate (2.43 g, 13.0 mmole, 92%);

υ_{max} (film) 3650 to 2150 ($\overset{+}{N}H_3$ and OH) and 1750 cm^{-1} (lactone);

δ_{PMR} (200 MHz; D_2O) 1.98-2.18 (1H, m, $\underline{H}CHCH_2CO$), 2.40-2.61 (1H, m, $CH\underline{H}CH_2CO$), 2.62-2.8 (2H, m, $C\underline{H}_2CO$), 3.2-3.49 (2H, m, $NC\underline{H}_2$) and 5.0-5.2 (1H, m, $\underline{H}CO$);

δ_{CMR} (15 MHz; D_2O and dioxane) 28.78 ($\underline{C}H_2CH_2CO$), 29.62 ($\underline{C}H_2CO$), 43.55 ($N\underline{C}H_2$), 78.58 ($H\underline{C}O$) and 178.70 ($\underline{C}=O$);

TLC: Rf = 0 (solvent system H).

N.B. A second (minor) set of signals were detected on ^{13}C-NMR, which was believed to be the acyclic acid, with peaks at δ 29.62, 30.4, 45.12, 67.6 and 181.70.

(B) By the reaction of a protected amino epoxide (272) with diethyl sodiomalonate

A solution of sodium ethoxide was carefully prepared by the addition of 50% sodium hydride (720 mg, 15 mmole) to ethanol (15 ml). This solution was stirred rapidly in an ice-bath and diethyl propanedioate (1.81 ml, 12 mmole) was added. The white suspension was stirred for 10 minutes and then refluxed for 15 minutes. 2-(2,3-Epoxypropyl)-1H-isoindole-1,3(2H)-dione (2.03 g, 10 mmole) was added to the mixture, in portions, over 25 minutes. After refluxing for a total of 5 hours, the dark-brown solution was cooled and concertrated to dryness. To the residue was added 6 N aqueous hydrochloric acid (30 ml) and heated under reflux for one hour. After cooling, the mixture was washed with ethyl acetate. The aqueous layer was separated and evaporated to leave a semi-solid residue, which was redissolved in water and purified by passing through a Dowex 50W X8 column. The aqueous eluant containing required product was evaporated to afford the title salt as a brown solid (1.52 g, 10 mmole, 100%).

IR and NMR (60 MHz) spectra of this compound were identical to those reported above.

5-[(Benzoylamino)methyl]dihydro-2(3H)-furanone (253)

The general procedure (E) for N-benzoylation of ammonium salts was used. Thus the title amide was obtained as a light yellow solid (483 mg, 2.21 mmole, 68%);

υ_{max} (film) 3300 (NH), 1750 (lactone C=O), 1630 and

1520 cm^{-1} (CONH);

δ_{PMR} (200 MHz; $CDCl_3$) 1.95-2.12 (1H, m, $\underline{H}CHCH_2CO$), 2.28-2.48 (1H, m, $C\underline{H}CH_2CO$), 2.52-2.62 (2H, m, $C\underline{H}_2CO$), 3.42-3.62 (1H, m, $NC\underline{H}$), 3.84-4.02 (1H, m, $HNC\underline{H}$), 4.63-4.81 (1H, m, $\underline{H}CO$), 6.68 (1H, broad singlet, $N\underline{H}$) and 7.3-7.6 and 7.7-7.8 (5H, m, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 24.87 ($\underline{C}H_2CH_2CO$), 28.65 ($\underline{C}H_2CO$), 43.55 ($\underline{C}H_2N$), 79.82 ($H\underline{C}O$), 127.47, 128.78, 132.03, 134.2 (6 x aromatic carbon atoms), 168.65 (amide $\underline{C}$=O) and 177.67 (lactone $\underline{C}$=O);

[Found: C, 64.9; H, 6.1; N, 6.4; $C_{12}H_{13}NO_3 \cdot 0.1H_2O$ (221) requires C, 65.2; H, 6.0; N, 6.3%];

TLC: Rf = 0.5 (solvent system H).

2-(2-Propenyl)propanedioic acid (255)

A solution of sodium hydroxide (6.1 g, 100 mmole) in water (10 ml) was stirred and diethyl 2-(2-propenyl) propanedioate (10 g, 50 mmole) was added, slowly. The resulting mixture was allowed to stand at room temperature for two days. Then the mixture was acidified to pH 1 with concentrated hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic layer was separated, dried and evaporated to leave the title acid as a white solid (2.85 g, 19.8 mmole, 40%);

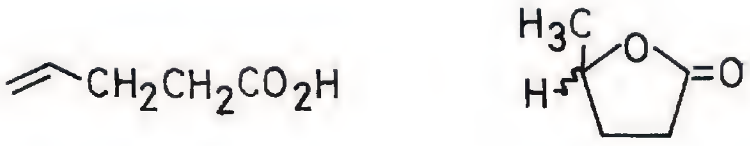
υ_{max} (Nujol) 3300-2500 (OH), 1700 (C=O) and 1620 cm^{-1} (C=C);

δ_{PMR} (200 MHz; $CDCl_3$) 2.7 (2H, t, $\underline{J}$ = 3.5 Hz, $=-C\underline{H}_2$), 3.55 (1H, t, $\underline{J}$ = 3.5 Hz, $CH_2C\underline{H}$), 5.12 (2H, m, $C\underline{H}_2$=C) and 5.78 (1H, m, $C\underline{H}$=C);

δ_{CMR} (15 MHz; acetone-d^6 and TMS) 33.59 (=-$\underline{C}H_2$), 51.82 ($CH_2\underline{C}H$), 117.70 ($\underline{C}H_2$=CH), 135.67 (CH_2=$\underline{C}H$) and 171.21 ($\underline{C}O_2H$);

TLC: Rf = 0.2 (solvent system J; a streaky trace).

<u>4-Pentenoic acid (248) and dihydro-5-methyl-2(3H)-furanone (256)</u>



(248) (256)

2-(2-Propenyl)propanedioic acid (4.1 g, 28.3 mmole) was heated in an oil-bath at 140^0 for one hour. During the reaction, the solid melted and gas evolved. The <u>title compounds</u> were isolated as a brown liquid in a 3 to 1 mixture (2.8 g, 28.1 mmole, 99%);

<u>Data on the title acid</u>:-

ν_{max} (film) 3600 to 2400 (CO_2H), 1690 (acid C=O) and 1622 cm^{-1} (C=C);

δ_{PMR} (200 MHz; $CDCl_3$) 2.22-2.59 (4H, m, $C\underline{H}_2C\underline{H}_2CO$), 4.9 to 5.12 (2H, m, $C\underline{H}_2$=CH) and 5.7-5.9 (1H, m, CH_2=$C\underline{H}$);

δ_{CMR} (15 MHz; $CDCl_3$) 28.58 ($\underline{C}H_2CH_2CO$), 33.46 ($\underline{C}H_2CO$), 116.01 ($\underline{C}H_2$=CH), 136.84 (CH_2=$\underline{C}H$) and 179.42 (acid $\underline{C}$=O);

TLC: Rf = 0.25 (solvent system J; streaky trace);

Data on the title lactone:-

υ_{max} (film) 1750 cm^{-1} (lactone)

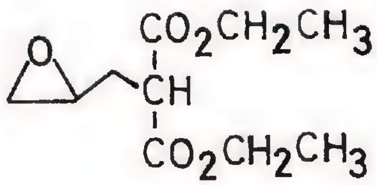
δ_{PMR} ($CDCl_3$) 1.4 (3H, d, J 3 Hz, $\underline{C}H_3$), 2.22 to 2.59 (4H, m, $C\underline{H}_2C\underline{H}_2CO$) and 4.5 to 4.7 (1H, m, $H\underline{C}O$),

δ_{CMR} ($CDCl_3$) 21.02 ($\underline{C}H_3$), 29.23 ($\underline{C}H_2CH_2CO$), 29.75 ($\underline{C}H_2CO$), 77.73 ($H\underline{C}O$) and 178.31 (lactone $\underline{C}$=O);

TLC: Rf = 0.6 (solvent system J).

N.B. The two components were not separated. Due to the differences in infrared absorptions, chemical shifts and TLC behaviours of the two compounds, it was possible to make the above assignments (IR, NMR and TLC) for each component of the mixture.

Diethyl 2-(2,3-epoxypropyl)propanedioate (257)



(257)

The title epoxide was prepared according to the general procedure (G) for epoxidation of alkenes as a light yellow oil (2.1 g, 9.65 mmole, 97%);

υ_{max} (film) 1720 cm^{-1} (ester);

δ_{PMR} (200 MHz; $CDCl_3$) 1.1 (6H, 2xt, J = 7 Hz, 2 x $CH_2C\underline{H}_3$), 1.92-2.1 (1H, m, $\underline{H}CHCH$), 2.2-2.38 (1H, m, $HC\underline{H}CH$), 2.5-2.58, 2.7 to 2.82 and 2.98-3.1 (3H, 3xm, 3 x epoxide

protons), 3.42-3.6 (1H, m, HCHC$\underline{H}$) and 4.22 (4H, q, $\underline{J}$ = 7 Hz, 2 x C$\underline{H}_2$CH$_3$);

δ_{CMR} (15 MHz; CDCl$_3$) 14.06 (CH$_2\underline{C}$H$_3$), 31.77 (H$\underline{C}$HCH), 47.33 (HCH$\underline{C}$H), 49.15 and 49.93 (2 x epoxide carbon atoms), 61.78 (O$\underline{C}$H$_2$CH$_3$) and 169.27 ($\underline{C}$=O);

TLC: Rf = 0.25 (solvent system M);

[Found: C, 54.5; H, 7.0 ; $C_{10}H_{16}O_5 \cdot 0.3H_2O$ (221.6) requires C, 54.2; H, 7.5%].

Diethyl 2-(3-azido-2-hydroxypropyl)propanedioate (258) and ethyl 5-(azidomethyl)-tetrahydro-2-oxo-3-furancarboxylate (259)

A solution of sodium azide (3.60 g, 56 mmole) was added to a solution of diethyl 2-(2,3-epoxypropyl)propanedioate (11.86 g, 55.0 mmole) in ethanol (50 ml), at room temperature. Then the solution was refluxed for 22 hours. The resulting golden yellow solution was concentrated to remove the ethanol. The residue was partitioned between ethyl acetate and dilute hydrochloric acid. The organic layer was separated, washed, dried and evaporated to leave the title compounds as a brown syrup (8.0 g);

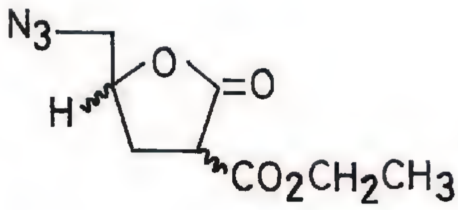
υ_{max} (film) 3650 to 3300 (OH), 2100 (N$_3$), 1780 (lactone C=O) and 1730 cm^{-1} (ester (C=O);

δ_{PMR} (60 MHz; CDCl$_3$) 1.28 (3H, t, $\underline{J}$ = 6 Hz, CH$_2$C$\underline{H}_3$), 1.7-2.8 (3H, m, C$\underline{H}_2$C$\underline{H}$), 3.2-3.65 (2H, m, NC$\underline{H}_2$), 3.9-4.39 (2H, q, $\underline{J}$ = 6 Hz, OC$\underline{H}_2$CH$_3$), 4.5-4.9 (1H, m, $\underline{H}$CO) and 6.5 (1H, broad singlet, O$\underline{H}$);

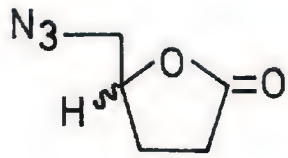
TLC: Rf = 0.73 (solvent system L, elongated spot).

N.B. The two components were not separated and used in the next stage of the synthesis without further purification (see p.257).

Ethyl 5-(azidomethyl)-tetrahydro-2-oxo-furancarboxylate (259) and 5-(azidomethyl)dihydro-2(3H)-furanone (251)



(259)



(251)

A mixture of diethyl 2-(3-azido-2-hydroxypropyl)-propanedioate and ethyl 5-(azidomethyl)-tetrahydro-2-oxo-3-furancarboxylate (8.0 g) was dissolved in trifluoroacetic acid (6 ml). After stirring for one hour at room temperature, the solvent was removed under reduced pressure to leave a brown gum. The crude product was purified on a silica gel column, eluting with a mixture of petrol ether 40-60^{o} and ethyl acetate (9:1, 4:1 and finally 2:1). The fractions containing the faster moving spot were combined and evaporated to leave the title furancarboxylic ester as a light brown gum (5.0 g, 23.5 mmole, 45%);

υ_{max} (film) 2100 (N_3), 1770 (lactone C=O) and 1720 cm^{-1} (ester C=O);

δ_{PMR} (200 MHz; $CDCl_3$) 1.28 (3H, t, $\underline{J}$ = 6 Hz, $CH_2C\underline{H}_3$), 2.58 to 2.72 (2H, m, $C\underline{H}_2CHCO$), 2.78 (1H, t, $\underline{J}$ = 4 Hz, $C\underline{H}CO$), 3.4 to 3.7 (2H, m, $NC\underline{H}_2$), 4.22 (2H, q, $\underline{J}$ = 6 Hz, $OC\underline{H}_2CH_3$)

and 4.6 to 4.78 (1H, m, HCO);

TLC: Rf = 0.41 (solvent system J).

Then the column was eluted with ethyl acetate. The fractions containing the slower running spot were combined and evaporated to leave the title azidolactone (251) as a light brown oil (1.67 g, 7.8 mmole, 14%);

IR & NMR spectra and TLC of this compound were identical with those measured for the compound prepared previously (see p. 249).

(S)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (260)

(A) Using phase-transfer conditions

The method described by Takano[243b] for oxidative cleavage of 1,2:5,6-bis-O-(1-methylethylidene)-D-mannitol (266) was used to give the title compound as a light brown oil (317 mg, 2.44 mmole, 100%);

υ_{max} (film) 3420 (OH) and 1735 cm^{-1} (C=O);

δ_{PMR} (60 MHz; $CDCl_3$) 1.35 and 1.40 (6H, 2s, CH_3-C-CH_3), 3.5-4.3 (3H, m, CH_2CH) and 9.74 (1H, d, J 2 Hz, CHO).

(B) Using lead tetraacetate

The procedure reported by Baer et al[262a] for oxidative cleavage of 1,2:5,6-bis-O-(1-methylethylidene)-D-mannitol (266) was followed to give the title compound as light brown oil (491 mg, 3.77 mmole, 77%); both IR and NMR spectra were identical to those reported above.

1,2:5,6-Bis-O-(1-methylethylidene)-D-mannitol (266) and 1,2:3,4:5,6-tris-O-(1-methylethylidene)-D-mannitol (267)

The method reported by Chittenden[260] for acetalation of D-mannitol was used. The crystalline residue obtained from the reaction was recrystallized from dibutyl ether to give

the <u>title diisopropylidene</u> compound as a white solid (5.25 g, 28.8 mmole, 42%);

m.p. 115^{o} (lit.[325] m.p. 118-120^{o});

$[\alpha]_D^{25}$ +1.17^{o} (C=0.65, H_2O) [lit.[325] $[\alpha]_D$ +1.2^{o} (H_2O)];

υ_{max} (Nujol) 3400 (OH) and 1735 and 1630 cm^{-1} (C-O-C, weak);

δ_{PMR} (60 MHz; $CDCl_3$) 1.4 and 1.5 (12H, 2s, 2 x $C\underline{H}_3$-C-$C\underline{H}_3$), 2.9 (2H, broad singlet, 2xOH), and 3.6-4.35 (8H, m, 2 x $C\underline{H}_2$ $C\underline{H}C\underline{H}$);

δ_{CMR} (15 MHz; $CDCl_3$) 25.2 and 26.7 (2 x $H_3\underline{C}$-C-CH_3), 75.0 ($\underline{C}$-1 and $\underline{C}$-6), 77.2 ($\underline{C}$-3 and $\underline{C}$-4), 79.2 ($\underline{C}$-2 and $\underline{C}$-5) and 109.5 (O-$\underline{C}$-O);

TLC: Rf = 0.75 (solvent system I).

The filtrate of above recrystallization was evaporated to a small volume and put onto a silica gel column, eluting with a mixture of 1,2-dimethoxyethane and petrol ether 40-60^{o} (1:1). The faster running fractions were combined and evaporated to leave the <u>title triisopropylidene compound</u> as a white crystalline residue (5.17 g, 19.7 mmole, 28%);

m.p. 67^{o} (lit.[260] m.p. 66-68^{o});

$[\alpha]_D$ + 10^{o} (0.5; EtOH) [lit.[260] $[\alpha]_D^{23}$ + 11.3^{o} (C=3.6; EtOH)];

υ_{max} (Nujol) 1738 and 1620 cm^{-1} (C-O-C);

δ_{PMR} (100 MHz; $CDCl_3$) 1.36, 1.38, 1.40, 1.42 (18H, 4s, 3 x $\underline{H}_3CCC\underline{H}_3$), and 3.62-4.4 (8H, m, 2 x $C\underline{H}_2C\underline{H}C\underline{H}$);

δ_{CMR} (15 MHz; $CDCl_3$) 24.8, 25.2, 25.5, 26.5, 26.7, 27.5 (6 x $\underline{C}H_3C$), 75.2 and 75.4 ($\underline{C}$-1 and $\underline{C}$-6), 76.3 and 76.5 ($\underline{C}$-3 and $\underline{C}$-4), 79.3 and 79.6 ($\underline{C}$-2 and $\underline{C}$-5), and 109.5, 109.8 and 110.4 (3 x O-$\underline{C}$-O);

TLC: Rf = 0.9 (solvent system U).

The slow fractions were combined and evaporated to leave a white crystalline residue, which was identified as the diisopropylidene compound.

(S)-2,2-dimethyl-4-[(2,4-dinitrophenyl)hydrazono]-methyl) -1,3-dioxolane (268)

(S)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (350 mg, 1.2 mmole) was dissolved in ethanol (6 ml) and refluxed with 2,4-dinitrophenylhydrazine (250 mg, 1.44 mmole), in the presence of glacial acetic acid (5 drops) for two hours. The light orange solid precipitated out on cooling was filtered. This crude solid was further purified by silica gel column chromatography. The fractions containing the required product were combined and evaporated to leave the title compound as an orange yellow solid (335 mg, 1.08 mmole, 90%);

m.p. 83°;

υ_{max} (Nujol) 3280 (NH), 1600 and 1580 cm^{-1} (C=N);

δ_{PMR} (200 MHz; acetone-d^6) 1.38 and 1.42 (6H, 2xs, 2xC$\underline{H}_3$), 2.82 (1H, d, $\underline{J}$ = 6 Hz, N$\underline{H}$), 4.03 (1H, dd, J = 8 and 6 Hz, $\underline{H}$CH), 4.28 (1H, dd, J = 8 and 6 Hz, HC$\underline{H}$), 4.78 (1H, ABq, J = 6 and 13 Hz, C$\underline{H}$C=), 7.96 (1H, d, aromatic proton), 8.01 (1H, d, aromatic proton), 8.41 (1H, dd, $\underline{J}$ = 3 and 3 Hz, aromatic proton), 8.98 (1H, d, J =3 Hz, $\underline{H}$C=);

δ_{CMR} (50 MHz; DMSO-d^6) 25.48 and 26.51 (2x$\underline{C}H_3$), 66.80 (O$\underline{C}H_2$CH), 75.07 ($\underline{C}$HC=), 109.70 (-$\underline{C}$=), 116.53, 122.87, 129.44, 129.82, 137.32, 144.74 (aromatic carbon

atoms) and 151.04 (C=N);

[Found: C, 46.3; H, 6.5; N, 17.5 ; $C_{12}H_{14}N_4O_6 \cdot 0.2H_2O$ (313.9) requires C, 45.9; H, 4.6; N, 17.8%];

TLC: Rf = 0.68 (solvent system T).

Ethyl (S)-(Z)-3-(2,3-dimethyl-1,3-dioxolanyl)-2-pentenoate (269)

A solution of diethyl ethoxycarbonylmethylphosphonate (849.4 mg, 3.8 mmole) in tetrahydrofuran (1 ml) was added dropwise, to a suspension of 80% sodium hydride (114.7 mg, 3.8 mmole) in dry tetrahydrofuran (6.3 ml), under nitrogen. Evolution of gas occurred immediately. After stirring at room temperature for a further 30 minutes, a solution of (S)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (490 mg, 3.77 mmole) in tetrahydrofuran (0.8 ml) was added, slowly. The almost colourless solution gradually became a suspension. The mixture was stirred for one hour and then diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate solution, brine, dried and evaporated to leave a light yellow oil. The crude product was purified by silica gel column chromatography to give the title ester as a pale yellow oil (402 mg, 2.0 mmole, 52%);

$[\alpha]_D^{25}$ + 3.02° (C=0.56, $CHCl_3$) [lit.[258c] $[\alpha]_D$ + 3° (C=2.1, $CHCl_3$)];

υ_{max} (film) 1722 (ester) and 1663 cm^{-1} (C=C);

δ_{PMR} (60 MHz; $CDCl_3$), 1.28 (3H, t, $\underline{J}$ = 7 Hz, $CH_2C\underline{H}_3$), 3.8 (2H, d, $\underline{J}$ = 7.8 Hz, O-$C\underline{H}_2$CH), 4.25 (2H, q, $\underline{J}$ = 7 Hz), 4.7 (1H, tdd, $\underline{J}$ = 7.8, 8 and 2.6 Hz O-$CH_2C\underline{H}$), 6.5 (1H, dd, $\underline{J}$ = 2.6 and 20 Hz, =$C\underline{H}$CO), 7.0 (1H, dd, $\underline{J}$ = 20 and 8 Hz,

$H\underline{C}=C$);

δ_{CMR} (15 MHz; $CDCl_3$) 14.1 ($CH_2\underline{C}H_3$), 25.7 and 26.4 ($H_3\underline{C}-C-\underline{C}H_3$), 60.6 ($O\underline{C}H_2CH_3$), 68.9 ($O\underline{C}H_2CH$), 76.5 ($-\underline{C}HO$), 110.4 ($H_3C-C-CH_3$), 122.7 ($=\underline{C}-CO$), 144.9 ($\underline{C}=CCO$) and 166.3 ($\underline{C}=O$);

[Found: C, 59.8; H, 7.8; $C_{10}H_{19}O_4$ (203.3) requires C, 60.0; H, 8.1%];

TLC: Rf = 0.74 (solvent system L).

Ethyl (S)-4,5-dihydroxy-pentanoate (271) and (S)-dihydro-5-(hydroxymethyl)-2(3H)-furanone (228)

10% Palladium-on-charcoal (196 mg) was added to a solution of ethyl (S)-(Z)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-pentenoate (196 mg, 0.97 mmole) in ethanol (10 ml). The mixture was hydrogenated under an atomsphere of hydrogen for 30 minutes, when the uptake of hydrogen became sluggish. After degassing the suspension was filtered. The filtrate was evaporated to leave an almost colourless oil (147 mg). NMR spectroscopy indicated some of the isopropylidene protecting group was lost during the operation. Thus the mixture was dissolved in trifluoroacetic acid (2 ml) and stored at room temperature for 30 minutes. Then the solvent was removed under reduced pressure to leave a yellow oil, which was further purified by column chromatography to afford the title lactone (228) as a light yellow oil (110 mg, 0.95 mmole, 98%);

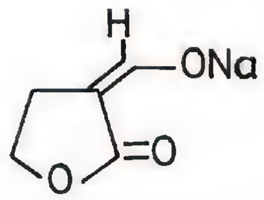
$[\alpha]_D$ + 33.1^o (C=0.56; EtOH), $[\alpha]_D$ was similar to that prepared by a different route (see p. 241);

IR spectrum was identical with the hydroxy lactone (228) prepared from L-glutamic acid (see p.241);

δ_{PMR} (200 MHz; $CDCl_3$) 2.02-3.8 (1H, m, $\underline{H}CHCH_2CO$), 4.02 (1H, m, OH), 2.5-3.4 (3H, m, $HC\underline{H}C\underline{H}_2CO$), 3.62 (1H, 2xd, $\underline{J}$ = 2.5 Hz, $HOC\underline{H}_2$), 3.90 (1H, 2xd, $\underline{J}$ = 2.5 Hz, $HOC\underline{H}_2$) and 4.62 (1H, m, $\underline{H}CO$).

Preparations of α-aminomethyl-γ-butyrolactones

Dihydro-3-(hydroxymethylene)-2(3H)-furanone (sodium salt) (296)



(296)

The synthesis of the title compound from butyrolactone (144) was carried out using the method described by Hutchinson.[277] The title salt was isolated as a creamy amorphous powder (6.4 g, 46.8 mmole, 81%);

υ_{max} (Nujol) 1690 (C=O) and 1650 cm^{-1} (C=C);

δ_{PMR} (D_2O + TSP) 2.6-3.1 (2H, m, $C\underline{H}_2CC=O$), 3.5-3.8 (1H, m, $\underline{H}CC=O$, aldehydic form), 4.2-4.6 (2H, m, $C\underline{H}_2$-O) and 8.55 (1H, s, $\underline{H}C=O$ and $=\!\!-_{\underline{H}}$);

δ_{CMR} (15 MHz; D_2O + dioxane) 24.4 ($\underline{C}H_2CC=O$, enolic form), 29.1 ($\underline{C}H_2CHC=O$, aldehydic form), 34.8 ($\underline{C}HC=O$, aldehydic form), 62.3 ($\underline{C}H_2$-O), 94.2 ($^{H}_{O}\!>\!\underline{C}=$, enolic form, 172.1 ($>C=\underline{C}C=O$, enolic form), 173.1 (lactone $\underline{C}$=O) and 181.2 (aldehyde $\underline{C}$=O);

TLC: Rf = 0.5 (after acidification with acetic acid; solvent system E).

N.B. A mixture of the aldehydic and enolic forms was observed in deuterium oxide solution, in both PMR and CMR. It was assumed the "salt" was still in the free enol state.

Dihydro-3-[(dimethylamino)methyl]-2(3H)-furanone (289)

The method described by Hutchinson[277] was followed. Thus dihydro-3-(hydroxymethylene)-2(3H)-furanone sodium salt (5.0 g, 36.8 mmole) reacted with dimethylammonium hydrochloride (5.98 g, 73.6 mmole), in the presence of sodium cyanotrihydroborate (4.6 g, 73.2 mmole) to give the title amine, an almost colourless oil, after column chromatography (2.53 g, 17.67 mmole, 48%);

υ_{max} (film) 1785 cm^{-1} (lactone C=O);

δ_{PMR} (200 MHz; $CDCl_3$) 2.18-2.4 (1H, m, $\underline{H}$CHCC=O), 2.42-2.65 (1H, m, HC$\underline{H}$CC=O), 2.58 and 2.60 (6H, 2xs, 2xC$\underline{H}_3$), 2.70-2.84 (2H, m, C$\underline{H}_2$N), 3.01-3.05 (1H, m, C$\underline{H}$C=O), and 4.20 to 4.5 (2H, m, C$\underline{H}_2$-O);

δ_{CMR} (15 MHz; $CDCl_3$) 27.73 ($\underline{C}H_2$CHCO), 34.32 (2 x N$\underline{C}H_3$), 43.81 ($\underline{C}$HCO), 52.21 ($\underline{C}H_2$N), 68.68 ($\underline{C}H_2$-O), and 177.08 ($\underline{C}$=O);

TLC: Rf = 0.15 (solvent system D).

Dihydro-3-[(dimethylamino)methyl]-2(3H)-furanone, hydrochloride (299a)

Concentrated hydrochloric acid (1.5 ml) was added to a solution of dihydro-3-[(dimethylamino)methyl]-2(3H)-furanone (1.52 g, 10.6 mmole) in methanol (10 ml). After standing at room temperature for one hour, the solution was concentrated to leave a semi-solid syrup, which was triturated with diethyl ether to leave the title hydrochloride as a white solid (1.51 g, 8.45 mmole, 80%);

m.p. 185^{o} (lit.[277] m.p. 190-190.5^{o});

υ_{max} (Nujol) 3650-2100 (H_2O + $\overset{+}{N}H\overset{-}{Cl}$), and 1760 cm^{-1} (lactone C=O);

δ_{PMR} (200 MHz; D_2O) 2.02-2.4 (1H, m, $\underline{H}CHCC=O$), 2.60-2.90 (1H, m, $HC\underline{H}CC=O$), 2.64 and 2.67 (6H, 2xs, $2xCH_3$) and 3.0-3.5 (3H, m, $NC\underline{H}_2C\underline{H}C=O$);

δ_{CMR} (50 MHz; D_2O + dioxane) 27.66 and 30.84 ($\underline{C}H_2CHC=O$), 35.31 and 37.12 (2 x $N\underline{C}H_3$), 42.58 and 44.16 ($\underline{C}HC=O$), 51.2 ($\underline{C}H_2N$), 65.06 and 68.71 ($\underline{C}H_2$-O), 170.10 and 180.08 ($\underline{C}$=O);

N.B. Both lactone (299a) and open-chain form (299b) were observed, especially in deuterium oxide solution. It was clearly defined in the CMR spectrum.

Dihydro-3-[[(2,4-dinitrophenyl)hydrazono]methyl]-2(3H)-furanone (300)

The general procedure (I) for preparation of hydrazones was used to give the title compound as an orange colour solid (901 mg, 3.1 mmole, 84%);

m.p. 94^o;

υ_{max} (Nujol) 3340 (NH), 1770 (lactone), 1620 and 1580 cm^{-1} (C=N);

δ_{PMR} (60 MHz; DMSOd^6) 2.0-2.9 (3H, m, $C\underline{H}_2C\underline{H}CO$), 4.0-4.6 ($C\underline{H}_2O$), 8.1, 8.3 and 8.9 (3H, aromatic protons);

δ_{CMR} (15 MHz; DMSOd^6) 25.98 ($\underline{C}H_2CHCO$), 35.2 ($\underline{C}HCO$), 67.25 ($\underline{C}H_2O$), 116.5, 123.0, 129.9 137.3, 144.8 and 148.9 (6 x aromatic carbon atoms), 149.2 ($\underline{C}$=N) and 175.6 ($\underline{C}$=O);

[Found: C, 43.6; H, 3.5; N, 20.2 ; $C_{11}H_{10}N_4O_6$. 0.1 H_2O (296.0) requires C, 44.6; H, 3.4; N, 18.9%];

TLC: Rf = 0.7 (solvent system H).

Dihydro-3-(hydroxymethyl)-2(3H)-furanone (301)

A solution of dihydro-3-(hydroxymethylene)-2(3H)-furanone sodium salt (1.0 g, 7.4 mmole) in water (3.0 ml) was neutralized with 10% hydrochloric acid solution until pH 7. The solution was added dropwise to a rapidly stirred suspension of sodium tetrahydridoborate (182 mg, 4.8 mmole) in ethanol (5.0 ml), at 0^{o}. After the addition, the reaction mixture was stirred at room temperature for 30 minutes. Then the excess reducing agent was destroyed by the addition of dilute hydrochloric acid until the pH of the reaction mixture was 2. The resulting clear solution was evaporated to dryness. The residue was dissolved in trichloromethane and washed with brine. The organic layer was separated, dried and evaporated to afford the title alcohol as a pale yellow oil (0.47 g, 4.1 mmole, 55%);

υ_{max} (film) 3400 (OH) and 1740 cm^{-1} (lactone);

δ_{PMR} (60 MHz; $CDCl_3$) 1.8-3.0 (3H, m, $C\underline{H}_2C\underline{H}CO$), 3.3 (1H, s, OH), 3.45-3.95 (2H, m, $C\underline{H}_2OH$) and 4.0-4.45 (2H, m, $C\underline{H}_2O$);

δ_{CMR} (15 MHz; $CDCl_3$) 25.1 ($\underline{C}H_2CHCO$), 41.9 ($\underline{C}HCO$), 61.5 ($\underline{C}H_2OH$), 67.4 ($\underline{C}H_2O$) and 179.4 ($\underline{C}$=O);

TLC: Rf = 0.16 (solvent system D); Rf = 0.6 (solvent system A).

3-[(Benzoyloxy)methyl]dihydro-2(3H)-furanone (302)

The general procedure (F) for the O-benzoylation was used with the alcohol (301) to give the title compound as a light brown liquid (201 mg, 0.92 mmole, 53%);

υ_{max} (film) 1770 (lactone) and 1720 cm^{-1} (ester);

δ_{PMR} (60 MHz; $CDCl_3$) 2.0-2.7 (2H, m, $C\underline{H}_2CHCO$), 2.8-3.3 (1H, m, $C\underline{H}CO$), 4.1-4.55 (2H, m, benzoyl $C\underline{H}_2O$) and 4.5-4.8 (2H, m, lactone $C\underline{H}_2O$);

δ_{PMR} (200 MHz; $CDCl_3$) 2.18 to 2.99 (1H, m, $\underline{H}CHCHC{=}O$), 2.41 to 2.59 (1H, m, $HC\underline{H}CHC{=}O$), 2.97 to 3.11 (1H, m, $C\underline{H}C{=}O$), 4.21 to 4.36 (1H, m, $\underline{H}CH\text{-}O$), 4.36 to 4.50 (1H, m, $HC\underline{H}\text{-}O$), 4.58 and 4.77 (2H, dABq, $\underline{J}$ 5.8 and 4 Hz, $C\underline{H}_2\text{-}\underline{O}$ Benzoate), 7.42 to 7.50, 7.2 to 7.82 and 7.99 to 8.03 (5H, m, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 25.9 ($\underline{C}H_2CHCO$), 39.4 ($\underline{C}HCO$), 63.1 (benzoyl $\underline{C}H_2O$), 66.8 (lactone $\underline{C}H_2O$), 128.7, 129.8 and 133.5 (6 x aromatic carbon atoms), 166.5 (benzoyl $\underline{C}{=}O$) and 176.7 (lactone $\underline{C}{=}O$);

[Found: C, 65.4; H, 5.8; $C_{12}H_{12}O_4$ (220.2) requires C, 65.4; H, 5.5%];

TLC: Rf = 0.75 (solvent system N).

<u>Dihydro-3-[[[(4-methylphenyl)sulphonyl]oxy]methyl]-2(3H)-furanone (303)</u>

The general procedure [(L), conditions (i)] for $\underline{O}$-sulphonation was used with compound (301) to give the <u>title sulphonate</u> a light yellow oil, which solidified on standing (517 mg, 1.92 mmole, 16%);

m.p. 75-77^{o};

υ_{max} (film) 1770 (lactone), 1358 and 1158 cm^{-1} (S=O);

δ_{PMR} (60 MHz; $CDCl_3$) 2.0-3.3 (3H, m, $C\underline{H}_2C\underline{H}CO$), 2.5 (3H, s, $ArC\underline{H}_3$), 4.1-4.7 (4H, m, 2 x $C\underline{H}_2O$), 7.45 and 7.85 (4H, 2xd, $\underline{J}$ = 8 Hz, aromatic protons);

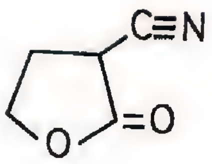
δ_{CMR} (15 MHz; $CDCl_3$) 21.74 ($Ar\underline{C}H_3$), 25.5 ($\underline{C}H_2CHCO$),

39.5 (CHCO), 66.99 (sulphonate CH_2O), 68.36 (lactone CH_2O), 128.2, 130.3, 132.4 and 145.6 (6 x aromatic carbon atoms) and 175.6 (C=O);

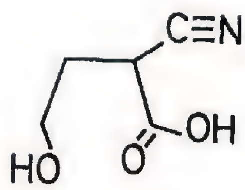
[Found: C, 53.4; H, 5.4; $C_{12}H_{14}O_5S$ (270.3) requires C, 53.3; H, 5.2%];

TLC: Rf = 0.7 (solvent system H); Rf = 0.5 (solvent system I).

3-Cyano-dihydro-2(3H)-furanone (306) and 2-cyano-4-hydroxy-butanoic acid (307)



(306)



(307)

Sodium cyanide (449 mg) was added to a stirred solution of 3-bromodihydro-2(3H)-furanone (1.0 g, 6.3 mmole) in N,N-dimethylformamide (10 ml). The resulting mixture was stirred at room temperature for 3 days. Then the suspension was diluted with ethyl acetate and washed thoroughly with water. The organic layer was separated, dried and evaporated to leave the title compounds as a brown oil (0.70 g, 6.3 mmole, 100%);

ν_{max} (film) 3500 (OH), 2250 (C≡N, very weak), 1770 (lactone C=O) and 1720 cm^{-1} (acid C=O);

δ_{PMR} (60 MHz; $CDCl_3$) 2.3 to 3.0 (2H, m, CH_2CHC=O), 3.05 to 3.5 (1H, m, CHC≡N) and 4.2 to 4.7 (2H, m, CH_2-O);

δ_{PMR} (200 MHz; $CDCl_3$) 1.7 (1H, broad s, OH), 2.38-2.7

(1H, m, $\underline{H}$CHCC=O, lactonic form), 2.62-2.9 (2H, m, $C\underline{H}_2$CC=O; open-chain form), 2.8-3.2 (1H, m, HC$\underline{H}$CC=O, lactonic form), 3.05-3.32 (1H, m, C$\underline{H}$C≡N, both forms), 4.21-4.42 (1H, m, $\underline{H}$CH-O, lactonic form) and 4.42-4.7 (2H, m, HC$\underline{H}$-O and $C\underline{H}_2$-OH, lactone and open-chain form);

δ_{CMR} (15 MHz; $CDCl_3$) 2 6•3 6 ($\underline{C}H_2$CC=O, open-chain), 31.77 ($\underline{C}H_2$CC=O, lactonic), 43.22 ($\underline{C}$HC=O, open-chain), 43.61 ($\underline{C}$HC=O, lactonic), 66.53 ($\underline{C}H_2$-O, lactonic) 66.92 ($\underline{C}H_2$-OH, open-chain), 115.88 and 116.14 (C≡N; both forms),169.59 (acid $\underline{C}$=O) and 173.82 (lactone $\underline{C}$=O);

[Found: C, 51.5; H, 4.7; N, 6.0 ; $C_5H_5NO_2 \cdot 0.4H_2O$ (118.3) requires C, 50.8; H, 4.9; N, 11.8%];

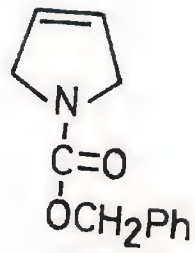
TLC: Rf = 0.2 (solvent system J).

N.B. Both lactonic and open-chain forms were produced.

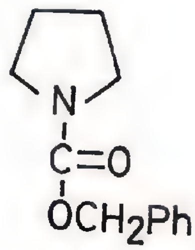
The CMR spectrum showed signals for both compounds.

Preparations leading to some bicyclic lactones

Phenylmethyl 3-pyrroline-1-carboxylate (312) and phenylmethyl pyrrolidine-1-carboxylate (313)



(312)



(313)

The general procedure (M) for the introduction of benzyloxycarbonyl-protecting group was followed. Thus the title compounds (312) and (313) were prepared from 3-pyrroline and pyrrolidine (suppled by Aldrich Chemical Co. Ltd., as a mixture of the two compounds, in a ratio of 75:25; 1.0 g, 14.5 mmole), as a light brown oil (2.95 g, 14.5 mmole, 100%);

υ_{max} (film) 1695 (N-$\underset{\|}{C}$O) and 1610 cm^{-1} (C=C);

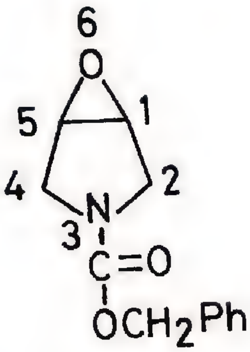
δ_{PMR} (200 MHz; $CDCl_3$) 1.8-1.9 (4H, m, $C\underline{H}_2C\underline{H}_2$, pyrrolidine); 3.3-3.5 (4H, m, 2 x $C\underline{H}_2N$, pyrrolidine), 4.2 (4H, s, 2 x $C\underline{H}_2N$, 3-pyrroline), 5.13 (2H, s, $C\underline{H}_2Ph$, pyrrolidine), 5.16 (2H, s, $C\underline{H}_2Ph$, 3-pyrroline), 7.36 (5H, m, $C\underline{H}_2\underline{PH}$, pyrrolidine) and 7.42 (5H, m, $CH_2\underline{Ph}$, 3-pyrroline);

δ_{CMR} (15 MHz; $CDCl_3$) 25.26 ($\underline{C}H_2\underline{C}H_2$, pyrrolidine), 46.09 ($\underline{C}H_2N$, pyrrolidine), 52.99 and 53.51 (2 x $\underline{C}H_2N$, 3-pyrroline), 66.66 ($\underline{C}H_2Ph$, pyrrolidine), 66.86 ($\underline{C}H_2$, 3-pyrroline), 125.97 ($\underline{C}=\underline{C}$, 3-pyrroline), 128.12, 128.70, 129.09,

129.55, 137.30 and 137.50 (aromatic carbon atoms, both compounds) and 154.94 ($\underline{C}$=O);

TLC: Rf = 0.65 (solvent system J).

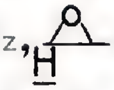
Phenylmethyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (314)



(314)

The title compound was prepared from phenylmethyl 3-pyrroline-1-carboxylate (3.06 g, 15.1 mmole) by the general method (G) for the epoxidation of alkenes. The product was obtained as a pale brown gum (1.37 g, 6.25 mmole, 42%);

υ_{max} (film) 1690 (carbamate C=O) and 740 cm^{-1} (epoxide);

δ_{PMR} (200 MHz; $CDCl_3$) 3.38 (1H, d, $\underline{J}$ = 2 Hz,  CH_2C=O), 3.43 (1H, d, $\underline{J}$ = 2 Hz,  CH_2NC=O), 3.84 (2H, d, $\underline{J}$ = 9 Hz, $C\underline{H}_2N$), 3.93 (2H, d, $\underline{J}$ = 9 Hz, $C\underline{H}_2NC$=O), 5.12 (2H, s, $C\underline{H}_2Ph$) and 7.38 (5H, m, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 47.26 ($\underline{C}H_2N$), 47.52 ($\underline{C}HNC$=O), 54.94 (), 55.53 ( CH_2NC=O), 67.12 ($\underline{C}H_2Ph$), 128.12, 128.31, 128.44, 128.70 and 130.20 (aromatic carbon atoms) and 155.66 ($\underline{C}$=O);

TLC: Rf = 0.30 (solvent system J).

Diethyl [4-hydroxy-1-[(phenylmethoxy)carbonyl]-3-pyrrolidinyl]propanedioate (315)

The general method (H) for the ring-open reaction of epoxide with diethyl 2-sodiopropanedioate was used. Thus the title hydroxy ester was prepared from phenylmethyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (2.94 g, 13.4 mmole) as a brown syrup (1.12 g, 2.96 mmole, 22%);

υ_{max} (film) 3400 (OH), 1710 (ester C=O) and 1680 cm^{-1} (carbamate C=O);

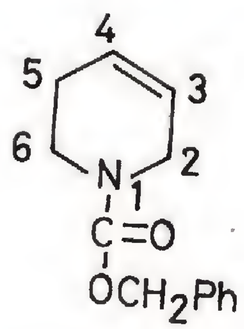
δ_{PMR} (200 MHz; $CDCl_3$) 1.28 (6H, t, $\underline{J}$ 7.6 Hz, 2 x $OCH_2C\underline{H}_3$), 2.62-2.82 (1H, m, $C\underline{H}CH(CO_2Et)_2$), 3.18-3.5 (4H, m, 2 x $C\underline{H}_2N$), 3.7-3.9 (2H, m, $HOC\underline{H}$ and $\underline{H}C(CO_2Et)_2$), 4.2 (4H, 2q, $\underline{J}$ 7.6 Hz, 2 x $OC\underline{H}_2CH_3$), 5.12 (2H, s, $C\underline{H}_2Ph$) and 7.37 (5H, m, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 13.99 ($OCH_2\underline{C}H_3$), 44.72 and 45.33 ($\underline{C}HC(CO_2Et)_2$, 47.91 ($\underline{C}(CO_2Et)_2$), 52.47 and 53.19 ($\underline{C}H_2N$), 62.04 ($O\underline{C}H_2CH_3$), 67.12 ($\underline{C}H_2Ph$), 72.13 and 72.91 ($\underline{C}HOH$), 128.05, 128.25, 128.70 and 136.84 (aromatic carbon atoms), 155.14 (carbamate $\underline{C}$=O), 168.29 and 168.88 (ester $\underline{C}$=O);

[Found: C, 59.8; H, 6.4; N, 4.0; $C_{19}H_{25}NO_7$ (379.4) requires C, 60.1; H, 6.6; N, 3.7%];

TLC: Rf = 0.75 (solvent system H).

Phenylmethyl 1,2,3,6-tetrahydropyridine-1-carboxylate (326)



(326)

This compound was prepared from 1,2,3,6-tetrahydropyridine (1.0 g, 12.03 mmole) using the general procedure (M) for the introduction of benzyloxycarbonyl-protecting group. The title compound was obtained as a colourless oil (1.8 g, 8.3 mmole, 69%);

υ_{max} (film) 1680 (carbamate C=O) and 1635 cm^{-1} (C=C);

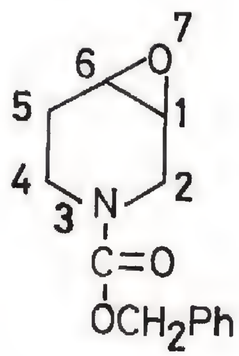
δ_{PMR} (200 MHz; $CDCl_3$) 2.02-2.2 (2H, m, $C\underline{H}_2CH_2N$), 3.56 (2H, t, $\underline{J}$ = 6 Hz, $CH_2C\underline{H}_2N$), 3.96 (2H, an apparent qnt, $\underline{J}$ = 3 Hz, $=CC\underline{H}_2N$), 5.16 (2H , s, $C\underline{H}_2Ph$), 5.52-5.71 (1H, m, $=C\underline{H}CH_2$), 5.72-5.88 (1H, m, $=C\underline{H}CH_2NC=O$) and 7.23-7.4 (5H, m, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$) 25.06 ($\underline{C}H_2CH_2N$), 40.49 ($CH_2\underline{C}H_2N$), 43.55 ($=CH\underline{C}H_2N$), 67.06 ($\underline{C}H_2Ph$), 124.41 ($=\underline{C}HCH_2CH_2N$), 125.45 ($=\underline{C}HCH_2N$), 128.12, 128.71, 137.17 (aromatic carbon atoms) and 155.73 ($\underline{C}$=O);

[Found: C, 69.1; H, 6.6; N, 6.0 ; $C_{13}H_{15}NO_2 \cdot 0.5H_2O$ (226.3) requires C, 69.0; H, 7.1; N, 6.2%];

TLC: Rf = 0.65 (solvent system J).

Phenylmethyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (330)



(330)

The <u>title epoxide</u> was prepared from phenylmethyl 1,2,3,6-tetrahydropyridine-1-carboxylate (1.05 g, 4.86 mmole) by general method (G) for epoxidation of alkenes. The product was obtained as a light yellow oil (0.89 g, 2.67 mmole, 55%);

υ_{max} (film) 1675 (carbamate C=O) and 740 cm^{-1} (epoxide);

δ_{PMR} (200 MHz; $CDCl_3$) 1.82-2.18 (2H, m, $C\underline{H}_2CH_2N$), 3.1-3.3 (2H, m, $\underline{H}\overset{O}{\wedge}\underline{H}$), 3.41-3.78 (2H, m, $CH_2C\underline{H}_2N$), 3.79-4.03 (2H, m, $C\underline{H}_2N$), 5.13 (2H, s, $C\underline{H}_2Ph$) and 7.3-7.5 (5H, m, aromatic protons);

δ_{CMR} (50 MHz; $CDCl_3$) 23.82 and 24.28 ($\underline{C}H_2CH_2N$), 37.50, 38.67, 42.51 and 43.88 (2 x $\underline{C}H_2N$), 50.06, 50.52, 52.40 and 53.12 ($\underline{C}\overset{O}{\wedge}\underline{C}$), 67.25 and 68.81 ($\underline{C}H_2Ph$), 128.05, 128.18, 128.70, 129.88, 135.41 and 136.84 (aromatic carbons), 153.38 and 155.66 (carbamate $\underline{C}$=O);

[Found: C, 63.8; H, 6.0; N, 5.3 ; $C_{13}H_{15}NO_3 \cdot 0.5H_2O$ (243.3) requires C, 64.5; H, 6.6; N, 5.7%];

TLC: Rf = 0.15 and 0.18 (solvent system J).

N.B. TLC and ^{13}C-NMR analysis indicated a mixture of two isomers, in a ratio of <u>ca</u>. 1:2.

<u>Diethyl 3,4-pyridinedicarboxylate (337)</u>

To 3,4-pyridinedicarboxylic acid (7.6 g, 45.5 mmole) in ethanol (64 ml) at 0^{o}, concentrated sulphuric acid (16.5 ml) was carefully added, and the mixture was heated under reflux for 24 hours. After cooling, water (10 ml) was slowly added to the dark brown reaction mixture. It was then neutralized with solid sodium hydrogen carbonate.

The mixture was extracted with ethyl acetate. The organic layer was separated, washed, dried and evaporated to leave the <u>title diester</u> as a brown oil (10.2 g, 45.5 mmole, 100%);

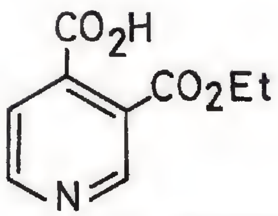
υ_{max} (film) 1720 cm^{-1} (ester C=O);

δ_{PMR} (200 MHz; $CDCl_3$) 1.4 (6H, 2xt, $\underline{J}$ = 7.6 Hz, 2 x $OCH_2C\underline{H}_3$), 4.42 (4H, 2xq, $\underline{J}$ = 7.6 Hz, 2 x $OC\underline{H}_2CH_3$), 7.51 (1H, d, $\underline{J}$ = 6 Hz, C-5$\underline{H}$), 8.85 (1H, d, $\underline{J}$ = 6 Hz, C-6$\underline{H}$) and 9.08 (1H, s, C-2$\underline{H}$);

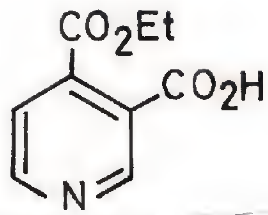
δ_{CMR} (50 MHz; $CDCl_3$) 14.01 and 14.10 (2 x $OCH_2\underline{C}H_3$), 62.08 and 62.37 (2 x $O\underline{C}H_2CH_3$), 121.85 ($\underline{C}$-5), 125.47 ($\underline{C}$-3), 140.63 ($\underline{C}$-4), 150.41 ($\underline{C}$-2), 152.69 ($\underline{C}$-6), 165.16 and 166.27 (2 x ester $\underline{C}$=O);

TLC: Rf = 0.43 (solvent system J).

<u>3-Ethoxycarbony-4-pyridinecarboxylic acid (338) and 4-ethoxycarbonyl-3-pyridinecarboxylic acid (339)</u>



(338)



(339)

Diethyl 3,4-pyridinedicarboxylate (12.36 g, 55.5 mmole) was suspended in water (104 ml) and a solution of sodium hydroxide (2.22 g, 55.5 mmole) in water (23 ml) was added. The resulting solution was stirred at room temperature for 1.5 hours. Then the mixture was acidified to pH 1

with concentrated hydrochloric acid. The solvent was removed and the residue was extracted with boiling tetrahydrofuran. The organic layer was evaporated to give the title carboxy-esters as a light brown solid (8.41 g, 43.1 mmole, 78%);

m.p. 125-160^{o} [not recrystallized; lit.[295] m.p. (of 4-ester) 131^{o}];

υ_{max} (Nujol) 3250 to 2500 (OH), 1725 (ester C=O) 1590 cm^{-1} (C=C and C=N);

δ_{PMR} (200 MHz; DMSO-d^6) 1.3 (3H, t, J 7.6 Hz, $OCH_2C\underline{H}_3$, β-carboxy), 1.32 (3H, t, J = 7.6 Hz, $OCH_2C\underline{H}_3$, γ-carboxy), 4.43 (2H, q, J = 7.6 Hz, $OC\underline{H}_2CH_3$), 7.62 (1H, d, J = 4.6 Hz, C-5H, β-carboxy), 7.68 (1H, d, J = 6 Hz, C-5H, γ-carboxy), 8.9 (1H, d, J = 6 Hz, C-6H), 8.97 (1H, s, C-2H, γ-carboxy) and 9.02 (1H, s, C-2H, β-carboxy);

δ_{CMR} (50 MHz; DMSO-d^6) 13.70 ($OCH_2\underline{C}H_3$), 61.64 ($O\underline{C}H_2CH_3$), 121.99 (C-5), 125.42 (C-3), 140.82 (C-4), 149.26 (C-2), 152.81 (C-6), 165.22 ($\underline{C}O_2H$) and 167.02 ($\underline{C}O_2Et$);

TLC: Rf = 0.1 (solvent system J, streaky trace):

N.B. NMR indicated a mixture of the γ- and β-carboxy isomers, in a ratio of ca. 9:1.

3-(Hydroxymethyl)-4-pyridinecarboxylic acid (340a) and 4-(hydroxymethyl)-3-pyridinecarboxylic acid (340b)

A mixture of 3-ethoxycarbonyl-4-pyridinecarboxylic acid and 4-ethoxycarbonyl-4-pyridinecarboxylic acid (4.23 g, 21.8 mmole) was dissolved in tetrahydrofuran (170 ml) and stirred in an ice-bath. The mixture was treated with

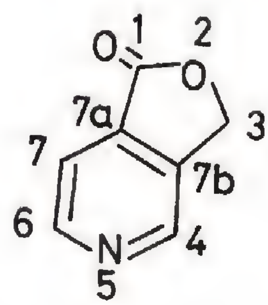
lithium tetrahydridoaluminate (1.47 g, 38.7 mmole), portion-wise, over 7 minutes and then stirred for a further 4 minutes. To the suspension was added water (4 ml), dropwise, carefully, to destroy the excess reducing agent. Then the mixture was stirred at room temperature for one hour. The solid was filtered and the filtre-cake was further extracted with more water. The aqueous filtrate and washings were combined and evaporated to a small volume, which was acidified to pH 2. The reddish-brown solution was evaporated to leave the title hydroxy-acids as a light brown gum (3.34 g, 21.8 mmole, 80%);

υ_{max} (film) 3700 to 2300 (OH), 1710 (C=O) and 1620 cm^{-1} (C=C, C=N and OH);

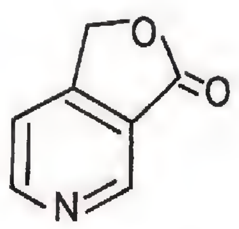
δ_{PMR} (60 MHz, D_2O + TSP) 5.02 (2H, s, $C\underline{H}_2O$), 8.25 (1H, d, $\underline{J}$ = 6 Hz, C-5$\underline{H}$), 8.85 (1H, d, $\underline{J}$ = 6 Hz, C-6$\underline{H}$), 9.02 (1H, s, C-2$\underline{H}$);

δ_{CMR} (15 MHz; D_2O + dioxane) 58.59 and 60.48 ($\underline{C}H_2OH$) 116.79 ($\underline{C}$-5) 124.15 ($\underline{C}$-3), 138.4 ($\underline{C}$-4), 141.07 ($\underline{C}$-2), 149.1 ($\underline{C}$-6) and 161.32 ($\underline{C}O_2H$).

Furo[3,4-C]pyridin-1(3H)-one (335) and Furo[3,4-C]-pyridin-3(1H)-one (336)



(335)



(336)

A mixture of 3-(hydroxymethyl)-4-pyridinecarboxylic acid and 4-(hydroxymethyl)-3-pyridinecarboxylic acid (3.3 g, 21.5 mmole) was dissolved in a mixture of water (50 ml) and tetrahydrofuran (50 ml). To the solution was added N,N'-dicyclohexylcarbodiimide (6.0 g, 29.1 mmole). The mixture was stirred at room temperature for 2 days. Then it was concentrated and filtered. The filtrate was concentrated to leave a gummy solid. The crude product was purified on a silica gel column (35 g), eluting with ethyl acetate and then a mixture of ethyl acetate and ethanol (2:1). Fractions containing the required product were combined and evaporated to leave the <u>title lactones</u> as a pale brown solid (396 mg, 2.94 mmole 10%);

υ_{max} (film) 1760 (lactone C=O) and 1600 cm^{-1} (C=C and C=N);

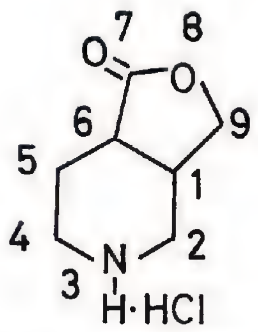
δ_{PMR} (200 MHz; $CDCl_3$) 5.38 and 5.46 (2H, 2xs, $C\underline{H}_2O$), 7.52 and 7.82 (1H, 2xd, $\underline{J}$ = 6 Hz, C-7$\underline{H}$), 8.9 (1H, d, $\underline{J}$ = 6 Hz, C-6$\underline{H}$), 8.98 and 9.2 (1H, 2xs, C-4$\underline{H}$);

δ_{CMR} (50 MHz; $CDCl_3$) 68.88 and 69.29 ($\underline{C}H_2O$) 117.53 and 118.84 ($\underline{C}$-7), 120.54 and 133.42 ($\underline{C}$-7b), 140.42 and 145.12 ($\underline{C}$-7a), 147.23 and 148.04 ($\underline{C}$-4) 149.88 and 153.24 ($\underline{C}$-6) and 169.36 (lactone $\underline{C}$=O);

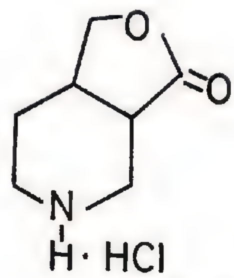
TLC: Rf = 0.24 and 0.36 (solvent system H), Rf = 0.38 and 0.55 (solvent system F);

N.B. Almost equal amount of both isomers by NMR and TLC analysis.

8-Oxa-3-azabicyclo[4.3.0]nonan-7-one hydrochloride (341) and 8-oxa-3-azabicyclo[4.3.0]nonan-9-one hydrochloride (342)



(341)



(342)

The general procedure (J) for hydrogenation (using platinum oxide for 24 hours) of unsaturated compounds was used. Thus a mixture of furo[3,4-C]pyridin-1(3H)-one and furo[3,4-C]pyridin-3(1H)-one (336 mg, 2.49 mmole) was reduced catalytically to give the title salts were obtained as a semi-solid gum (0.45 g, 2.56 mmole, 103%);

υ_{max} (film) 3600 to 2200 ($\overset{+}{N}H_4\overset{-}{C}l$) and 1740 cm^{-1} (lactone C=O);

δ_{PMR} (200 MHz; D_2O + TSP) 1.4-2.4 (3H, m, C-1H, C-5H and C-6H), 2.8-3.5 (4H, m, C-2H and C-4H), 3.5-3.81 (2H, m, C-7H_a and C-9H_a, C-1H and C-6H), 4.1-4.28 and 4.4-4.32 (1H, m, C-7H_b and C-9H_b);

δ_{CMR} (50 MHz; D_2O) 21.46 and 25.40 (C-5), 29.75 and 32.59 (C-1 + CH_2 and C-6 + CH_2), 39.07 and 39.89 (C-1 + C=O and C-6 + C=O), 42.40, 43.89, 44.68 and 45.46 (C-2 and C-4), 72.53 and 75.51 (CH_2O), 180.84 and 182.27 (lactone C=O);

TLC: Rf = 0.3 (solvent system H, streaky trace).

3-Benzoyl-8-oxa-3-azabicyclo[4.3.0]nonan-7-one (343) and 3-benzoyl-8-oxa-3-azabicyclo[4.3.0]nonan-9-one (344)

The title benzoates were prepared from a mixture of 8-oxa-3-azabicyclo[4.3.0]nonan-7-one hydrochloride and 8-oxa-3-azabicyclo[4.3.0]nonan-9-one hydrochloride (0.40 g, 2.25 mmole) by the general method for N-benzoylation of ammonium salts. The products were purified and separated by column chromatography. The faster moving spot was tentatively assigned as 3-benzoyl-8-oxa-3-azabicyclo[4.3.0]nonan-7-one, a light brown gum, with a yield of (0.13 g, 0.51 mmole, 23%);

υ_{max} ($CHBr_3$) 1770 (lactone C=O) and 1630 cm^{-1} (amide);

δ_{PMR} (200 MHz; $CDCl_3$) 1.7-2.3 (2H, m, C-5H), 2.5-3.2 (5H, m, C-1H , C-2H, C-4H or C-6H), 3.5-3.7 (1H, m, C-1H or C-6H) 4.1-4.7 (2H, m, CH_2O) and 7.3 to 7.5 (5H, m, aromatic protons);

δ_{CMR} (50 MHz; $CDCl_3$) 22.54 (C-5), 34.47 and 34.57 (C-2 and C-4), 37.93 (C-1 and C-6), 69.15 (CH_2O), 126.79, 128.60, 129.99, 135.34 (aromatic carbon atoms), 170.70 (amide C=O) and 177.01 (lactone C=O);

mass spectrum: M/Z 245 (M^+);

[Found: C, 65.9; H, 6.0; N, 5.3 ; $C_{14}H_{15}NO_3 \cdot 0.5H_2O$ (254.3) requires C, 66.1; H, 6.3; N, 5.5%];

TLC: Rf = 0.41 (solvent system H).

The slower moving spot was isolated as a yellow syrup, which was assigned to be 3-benzoyl-8-oxa-3-azabicyclo[4.3.0]nonan-9-one (0.11 g, 0.44 mmole, 20%);

υ_{max} ($CHBr_3$) 1780 (lactone C=O) and 163 cm^{-1} (amide);

δ_{PMR} (200 MHz; $CDCl_3$) 1.5-1.82 (2H, m, C-5$\underline{H}$), 1.83 to 2.02 (1H, m, C-6$\underline{H}$), 2.6-2.93 (4H, m, C-2$\underline{H}$ and C-4$\underline{H}$), 3.35 (1H, dd, $\underline{J}$ = 5 Hz, C-1$\underline{H}$), 4.05 (1H, d, $\underline{J}$ = 7.6 Hz, $\underline{H}$CHO), 4.30 (1H, dd, $\underline{J}$ = 5 Hz, HC$\underline{H}$O) and 7.3 to 7.5 (5H, m, aromatic prtons);

δ_{CMR} (50 MHz; $CDCl_3$) 26.40 ($\underline{C}$-5), 33.72 and 33.74 ($\underline{C}$-2 and $\underline{C}$-4), 39.68 ($\underline{C}$-1 and $\underline{C}$-6), 71.25 ($\underline{C}H_2O$), 127.17, 128.36, 129.79 and 135.52 (aromatic carbon atoms), 171.17 (amide $\underline{C}$=O) and 175.76 (lactone $\underline{C}$=O);

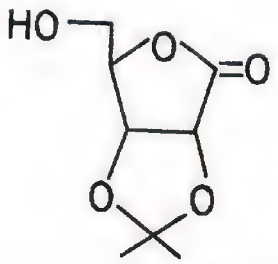
mass spectrum M/Z 244 (M^+-1);

[Found: C, 65.5; H, 6.2; N, 5.5 ; $C_{14}H_{15}NO_3 \cdot 0.55H_2O$ (255.2) requires C, 65.9; H, 6.3; N, 5.5%];

TLC: Rf = 0.25 (solvent system H).

Preparations leading to some amino sugar lactones

2,3-(1-Methylethylidene)-D-ribono-1,4-lactone (346)



(346)

The general procedure (A) for acetalation was used. Thus the title lactone was prepared from D-ribono-1,4-lactone (10.0 g, 66.5 mmole). Recrystallization from a mixture of 2-propanone and petrol ether 60-80^{o} (1:10) gave an off-white solid (5.4 g, 28.6 mmole, 44%);

m.p. 136-138^{o} (lit.[308] m.p. 138-139^{o});

$[\alpha]_D^{25}$ -56.9^{o} (C=0.52; pyridine); [lit.[308] $[\alpha]_D^{24^o}$ -65.7^{o} (C=2.13; pyridine)];

υ_{max} ($CHBr_3$) 3500 (OH) and 1760 cm^{-1} (lactone C=O);

δ_{PMR} (60 MHz; $CDCl_3$ + DMSO-d^6) 1.35 and 1.40 (6H, 2xs, $C{<}^{CH_3}_{CH_3}$), 4.25 (2H, dd, J = 2 and 13 Hz, C$\underline{H}_2$OH), 4.35 (1H, d, J=13 Hz, C-2$\underline{H}$), 4.55 (1H, collapsed t, C-4$\underline{H}$) and 4.75 (1H, dd, J=3 and 8 Hz, C-3$\underline{H}$);

δ_{PMR} (200 MHz, $CDCl_3$ + pyridine-d^5) 1.32 and 1.41 (6H, 2xs, $C{<}^{CH_3}_{CH_3}$), 4.23 (1H, dd, J = 2 and 10 Hz, C-5$\underline{H}_b$) 4.38 (1H, d, J = 10 Hz, C-5$\underline{H}_a$), 4.58 (1H, d, J = 8 Hz, C-2$\underline{H}$), 4.68 (1H, t, J = 3 Hz, C-4$\underline{H}$) and 4.92 (1H, dd, J= 3 and 8 Hz, C-3$\underline{H}$);

δ_{CMR} (15 MHz; pyridine-d^5) 22.59 and 24.54 ($>C<^{CH}_{\underline{C}H}$), 66.08 ($\underline{C}$-5), 68.22 ($\underline{C}$-3), 72.20 ($\underline{C}$-2), 75.45 ($\underline{C}$-4), 108.33 ($>\underline{C}<^{O}_{O}$) and 171.35 (lactone $\underline{C}$=O);

TLC: Rf = 0.80 (solvent system H).

<u>2,3-(1-Methylethylidene)-5-[(4-methylphenyl)sulphonyl]-D-ribono-1,4-lactone (347)</u>

This compound was prepared from 2,3-(1-methylethylidene)-D-ribono-1,4-lactone (1.13 g, 5.97 mmole) by the general method [(L), conditions (ii)] for O-sulphonation of alcohols. Thus the <u>title sulphonate</u> was obtained as white crystals (1.73 g, 5.03 mmole, 84%);

m.p. 117° (lit.[308] m.p. 117.5-118°);

$[\alpha]_D^{25°}$ -14.2 (C=0.46, acetone); [lit.[308] $[\alpha]_D^{24°}$ -15.8° (C=2.4, acetone)];

ν_{max} ($CHCl_3$) 1780 (lactone C=O), 1370 and 1160 cm^{-1} (SO_2);

δ_{PMR} (200 MHz; $CDCl_3$ + pyridine-d^5) 1.36 and 1.43 (6H, 2xs, $>C<^{CH_3}_{\underline{CH_3}}$), 2.43 (3H, s, $C\underline{H}_3Ph$), 4.21 (1H, dd, $\underline{J}$=2 and 13 Hz, C-5$\underline{H}_b$), 4.40 (1H, d, $\underline{J}$=13 Hz, C-5$\underline{H}_a$), 4.61 (1H, d, $\underline{J}$=8 Hz, C-2$\underline{H}$), 4.91 (1H, dd, $\underline{J}$ = 3 and 8 Hz, C-3$\underline{H}$), 4.99 (1H, d, $\underline{J}$ = 8 Hz, C-4$\underline{H}$), 7.32 and 7.90 (4H, 2xd, $\underline{J}$=6 and 6 Hz, aromatic protons);

δ_{CMR} (15 MHz; $CDCl_3$ + pyridine-d^5 + dioxane) 21.48 ($\underline{C}H_3Ph$), 24.21 and 25.91 ($>C<^{CH_3}_{\underline{C}H_3}$), 67.77 ($\underline{C}$-5), 73.30 ($\underline{C}$-3), 74.54 ($\underline{C}$-2), 75.06 ($\underline{C}$-4), 111.13 ($>\underline{C}<^{O}_{O}$), 128.44, 130.01, 133.91, 145.57 (aromatic carbon atoms) and 177.40 (lactone $\underline{C}$=O);

TLC: Rf = 0.28 (solvent system J).

5-Azido-5-deoxy-2,3-(1-methylethylidene)-D-ribono-1,4-lactone (348)

The title azide was prepared from 2,3-(1-methylethylidene)-5-[(4-methylphenyl)sulphonyl]-D-ribono-1,4-lactone (1.76 g, 8.27 mmole)by the method of Hanessian[306] as a brown syrup (370 mg, 1.74 mmole, 21%);

υ_{max} (film) 2120 (N_3) and 1790 cm^{-1} (lactone C=O);

δ_{PMR} (200 MHz; $CDCl_3$) 1.39 and 1.48 (6H, 2xs, $>C\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$), 3.70 (2H, dxq, J = 2 and 14 Hz, C-5H), 4.61 (1H, d, J = 6 Hz, C-2H), 4.64 (1H, t, J = 3 Hz, C-4H), 4.83 (1H, d, J = 6 Hz, C-3H);

δ_{CMR} (15 MHz; $CDCl_3$) 25.52 and 26.69 ($>C\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$), 52.53 ($CH_2N$), 75.26 ($C$-3), 78.25 ($C$-2), 80.40 ($C$-4), 113.86 ($>C\begin{smallmatrix}O\\O\end{smallmatrix}$) and 174.08 (lactone C=O);

TLC: Rf = 0.5 (solvent system H).

The product was still contaminated with N, N-dimethylformamide (ca. 0.7 equivalent).

5-Amino-5-deoxy-D-ribono-1,4-lactone hydrochloride (349)

The general procedure (J) for hydrogenation of azide was used. Thus the title hydrochloride was prepared from 5-azido-5-deoxy-2,3-(1-methylethylidene)-D-ribono-1,4-lactone (400 mg, 1.88 mmole) as a brown hygroscopic solid (300 mg, 1.64 mmole, 87%);

υ_{max} (Nujol) 3700 to 2200 ($\overset{+}{N}H_3$) and 1770 cm^{-1} (lactone C=O);

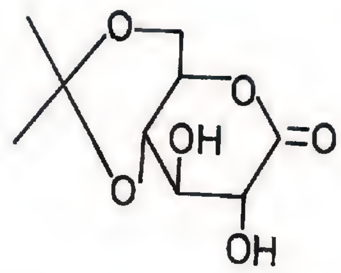
δ_{PMR} (200 MHz; D_2O + TSP) 3.42 (2H, dxq, J = 2 and 14 Hz, C-5H), 4.43 (1H, d, J = 6 Hz, C-2H) 4.85 (2H, C-3H

and C-4$\underline{H}$, obscured under D_2O peak);

δ_{CMR} (50 MHz; D_2O + TSP) 45.17 ($\underline{C}H_2N$), 72.27 ($\underline{C}$-3), 74.31 ($\underline{C}$-2), 76.83 ($\underline{C}$-4) and 177.74 (lactone $\underline{C}$=O);

TLC: Rf = 0 (solvent system H).

4,6-(1-Methylethylidene)-D-glucono-1,5-lactone (356)



(356)

The general procedure (A) for acetalation was followed. Thus the title compound was prepared form D-glucono-1,5-lactone (11.3 g, 63.5 mmole) as a golden yellow syrup (13.7 g, 63.5 mmole, 100%);

$[\alpha]_D^{25}$ +2.59^o (C=1.16, EtOAc);

ν_{max} (film) 3475 (OH) and 1715 cm^{-1} (δ-lactone C=O);

δ_{PMR} (200 MHz; $CDCl_3$) 1.4 and 1.44 (6H, 2xs, $C\underline{H}_3$-C-$C\underline{H}_3$), 3.02 (1H, d, $\underline{J}$ = 8 Hz, C-3-O$\underline{H}$; disappeared upon deuteration), 3.94-4.16 (3H, m, C-4H abd C-6$\underline{H}$), 4.22 (1H, dd, $\underline{J}$ = 1.5 and 8 Hz, C-2$\underline{H}$), 4.34 (1H, d, $\underline{J}$ = 8 Hz, C-3$\underline{H}$)and 4.48 [1H, ddd, $\underline{J}$ = (1.5, 8, 1.5 and 8 Hz), C-5$\underline{H}$];

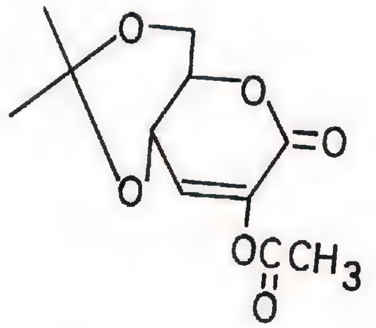
δ_{CMR} (50 MHz; $CDCl_3$) 26.83 and 27.23 ($\underline{C}H_3$-C-$\underline{C}H_3$), 67.89 ($\underline{C}$-6), 69.53 ($\underline{C}$-5), 76.60 ($\underline{C}$-3), 77.35 ($\underline{C}$-4), 80.97 ($\underline{C}$-2), 110.03 (CH_3-$\underline{C}$-CH_3) and 172.95 ($\underline{C}$=O);

[Found: C, 53.8; H, 7.5 ; $C_9H_{14}O_6$. 1 mole of $C_5H_{12}O_2$ (322.2) requires C, 52.2; H, 8.1%];

G.C. at 230° : Rt = 2.3 min.;

TLC: Rf = 0.82 (solvent system H).

2-Acetyl-4,6-(1-methylethylidene)-D-erythro-2-hexenono-1,5-lactone (357)



(357)

Using the general procedure (C) for O-acetylation of alcohols, this compound was prepared from 4,6-(1-methylethylidene)-D-glucono-1,5-lactone (2.0 g, 9.2 mmole). The crude product obtained was purified by silica gel column chromatography. The fractions eluted, which contained the required product, were combined and evaporated to leave the title acetate as an almost colourless syrup, which crystallized on drying (1.73 g, 7.2 mmole, 77%);

m.p. 57-58°;

$[\alpha]_D^{25}$ +33.27° (C=0.49, EtOAc);

ν_{max} (film) 1740 (acetate C=O), 1730 (δ-lactone C=O) and 1640 cm^{-1} (C=C);

δ_{PMR} (200 MHz; $CDCl_3$) 1.38 and 1.44 (6H, 2xs, CH_3-C-CH_3), 2.20 (3H, s, CH_3C=O), 3.8-4.3 (3H, m, C-5H and C-6H), 4.46 (1H, dd, J = 2 and 8 Hz, C-4H), 5.30 (1H, d, J = 2 Hz, C-3H);

δ_{CMR} (50 MHz; $CDCl_3$) 20.53 ($\underline{C}H_3C$=O), 25.08 and 26.72 ($\underline{C}H_3$-C-$\underline{C}H_3$), 67.66 ($\underline{C}$-6), 70.99 ($\underline{C}$-5), 76.59 ($\underline{C}$-4), 109.88 (CH_3-$\underline{C}$-CH_3), 110.46 (C-3; $\underline{C}$=C), 167.93 (acetate $\underline{C}$=O) and 169.92 (δ-lactone $\underline{C}$=O);

[Found: C, 54.3; H, 7.2 ; $C_{11}H_{14}O_6 \cdot 0.2H_2O$ (244.0) requires C, 54.1; H, 5.9%];

G.C. at 220^o : Rt = 5.8 min.;

TLC: Rf = 0.55 (solvent system F).

<u>4,6-(1-Methylethylidene)-2-[(4-methylphenyl)-sulphonyl]-D-erythro-2-hexenono-1,5-lactone (358)</u>

This compound eas prepared by the general procedure [(L), conditions (ii)] for <u>O</u>-sulphonation of alcohols. Thus 4,6-(1-methylethylidene)-D-glucono-1,5-lactone (2.0 g, 9.2 mmole) reacted with 4-methylbenzenesulphonyl chloride to give the <u>title sulphonate</u> as a light yellow syrup, which crystallized out on storage in the refrigerator (2.5 g, 7.1 mmole, 77%);

m.p. 61-64^o;

$[\alpha]_D^{25}$ +49.79^o (C=0.47, EtOAc);

υ_{max} (film) 1725 ($\underline{C}$=O), 1625 (C=C), 1350 and 1167 cm^{-1} (SO_2);

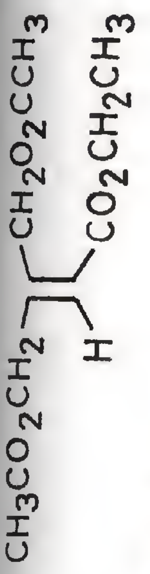
δ_{PMR} (200 MHz; $CDCl_3$) 1.38 and 1.48 (6H, 2xs, $C\underline{H}_3C$-$C\underline{H}_3$), 2.47 (3H, s, Ar$C\underline{H}_3$), 3.8-4.21 (3H, m, C-5$\underline{H}$ and C-6$\underline{H}$), 4.5 (1H, dd, $\underline{J}$ = 2 and 8 Hz, C-4$\underline{H}$), 5.18 (1H, d, $\underline{J}$ = 2 Hz, C-3$\underline{H}$), 7.36 and 7.89 (4H, 2xd, $\underline{J}$ = 8 Hz, aromatic protons);

δ_{CMR} (50 MHz; $CDCl_3$) 21.62 (Ar$\underline{C}H_3$), 25.17 and 27.39 ($\underline{C}H_3$-C-$\underline{C}H_3$), 67.84 ($\underline{C}$-6), 76.47 ($\underline{C}$-5), 77.14 ($\underline{C}$-4),

110.07 (CH_3-$\underline{C}$-CH_3), 110.04 ($\underline{C}$-3; $\underline{C}$=C), 128.12, 129.68, 133.54 and 145.09 (aromatic carbon atoms) and 167.06 ($\underline{C}$=O);

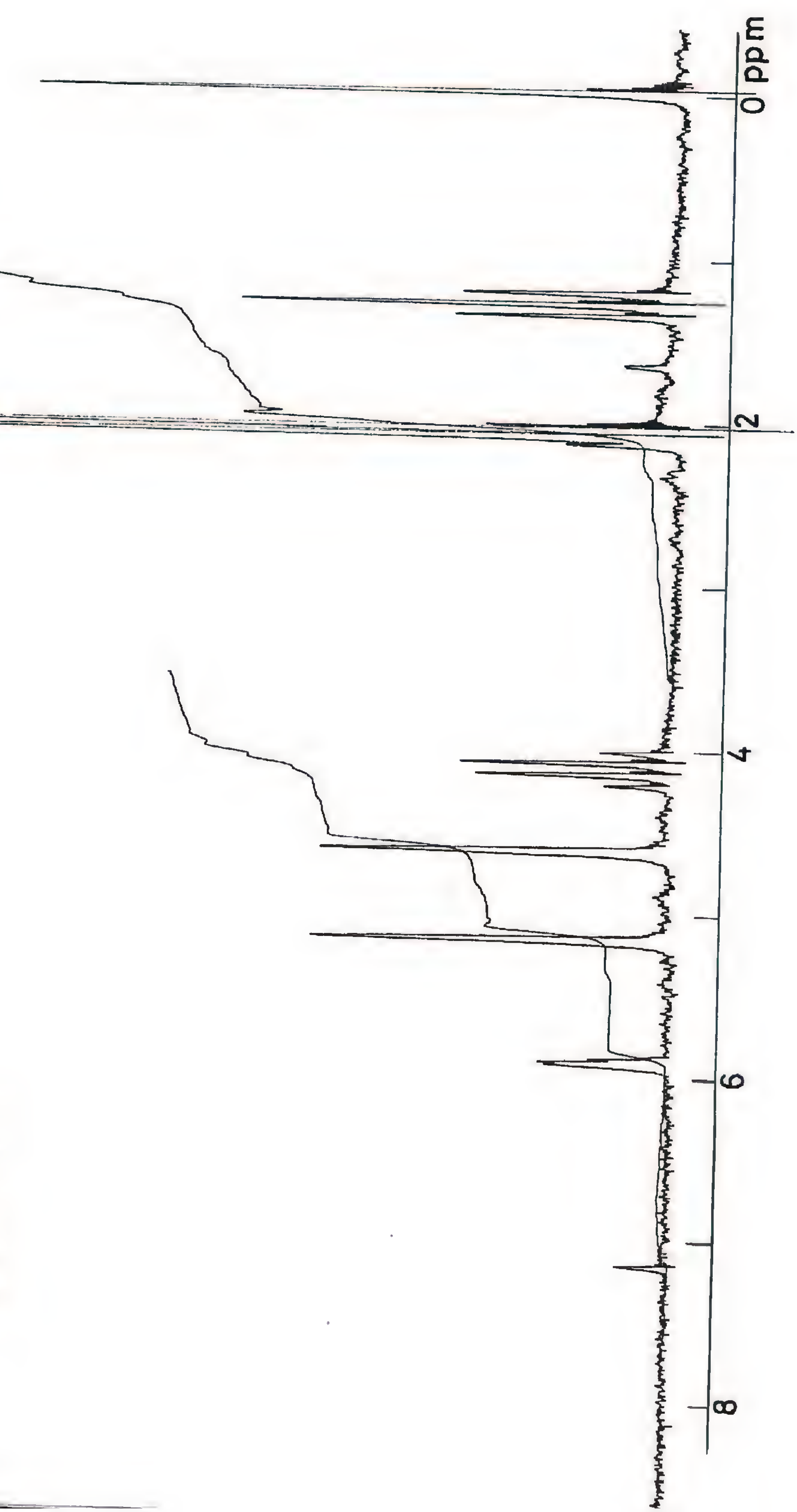
[Found: C, 53.3; H, 6.1 ; $C_{16}H_{18}O_7S$. 0.1 ($C_5H_{12}O_2$) (372.0) requires C, 53.3; H, 5.2%];

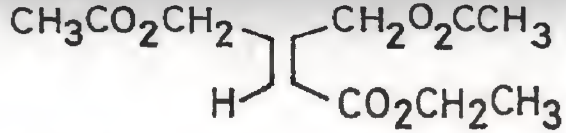
TLC: Rf = 0.6 (solvent system J).



(114)

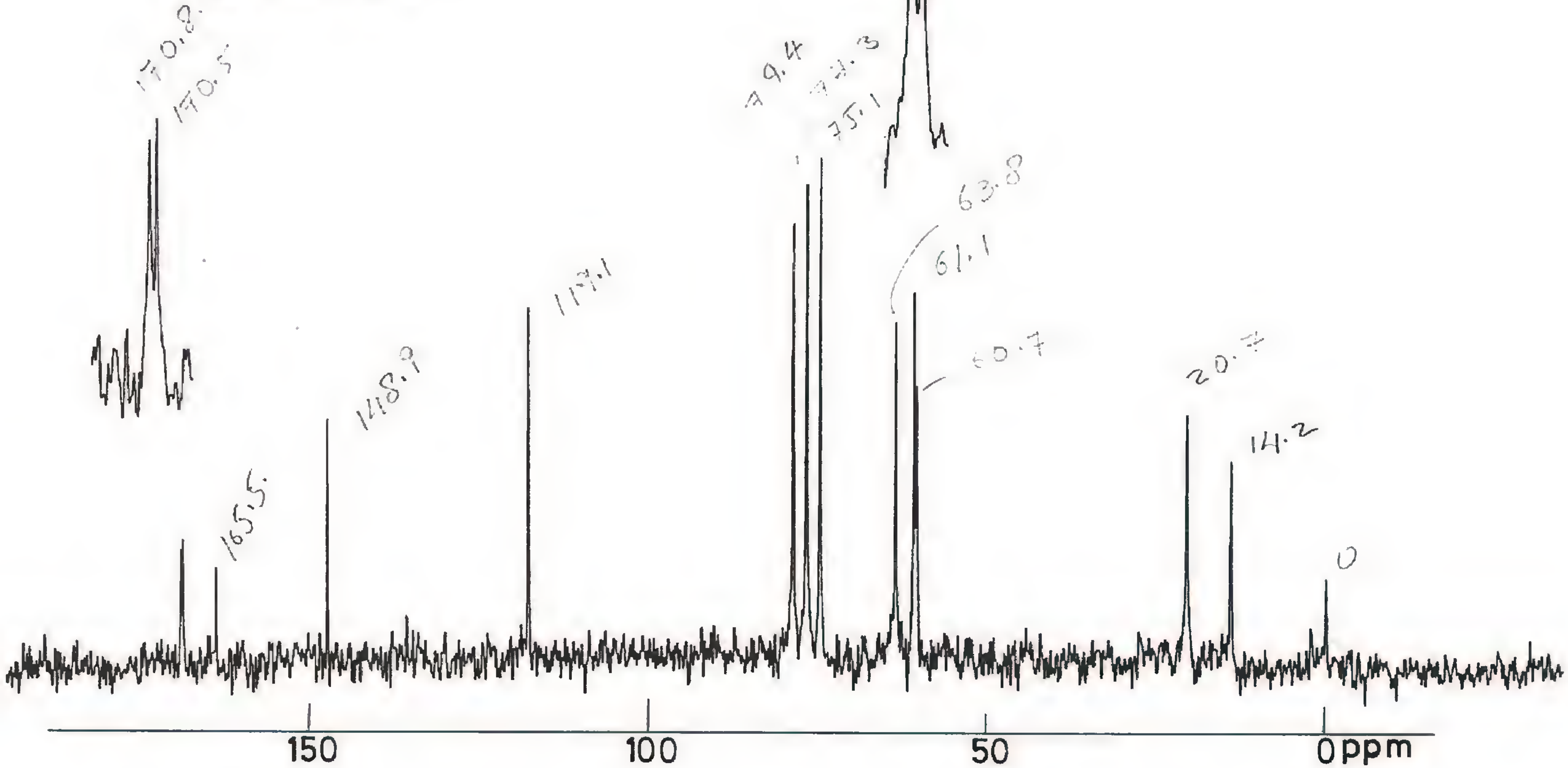
Spectrum P–1





(114)

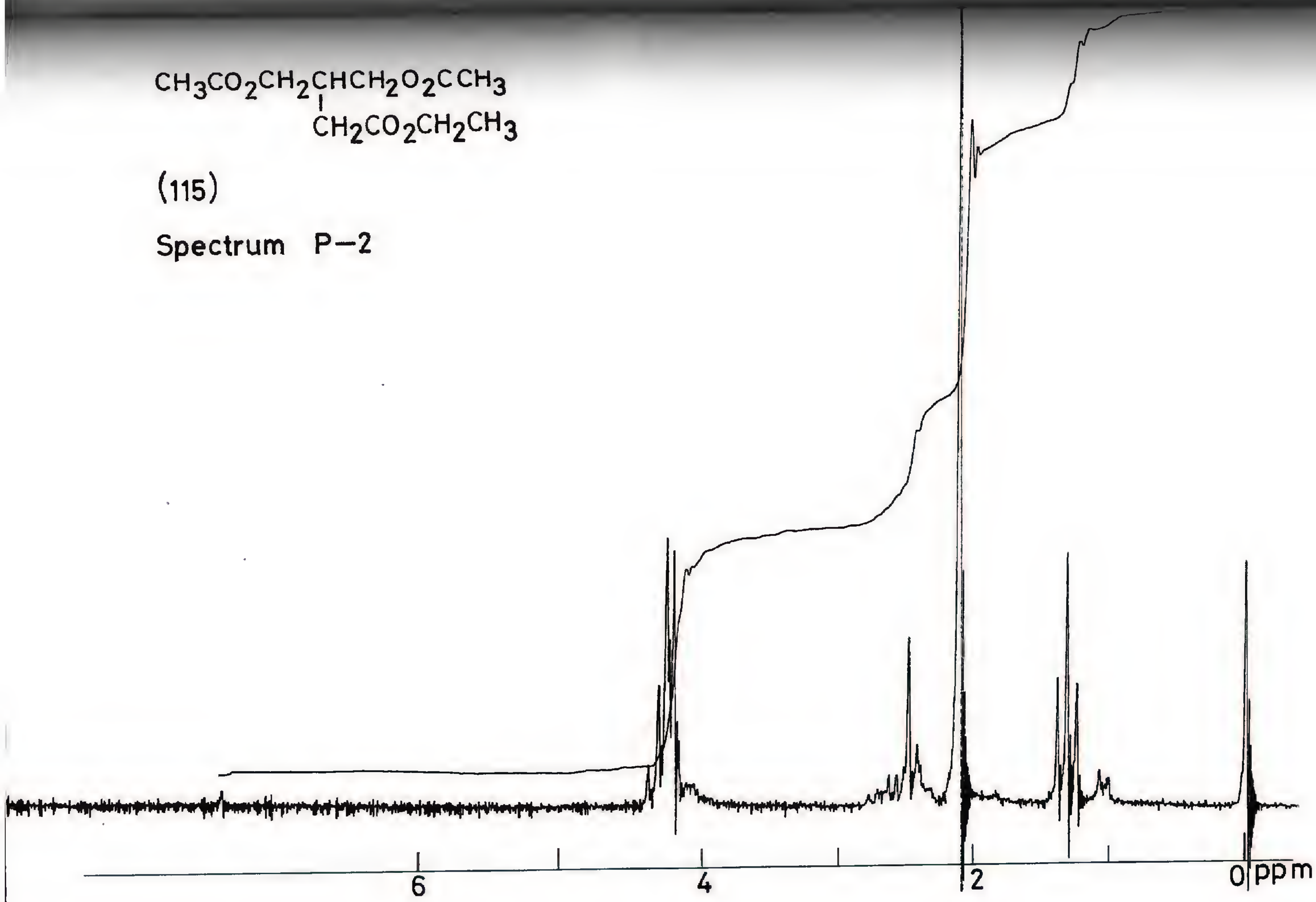
Spectrum C-1



$CH_3CO_2CH_2\underset{|}{C}HCH_2O_2CCH_3$
$\qquad\qquad CH_2CO_2CH_2CH_3$

(115)

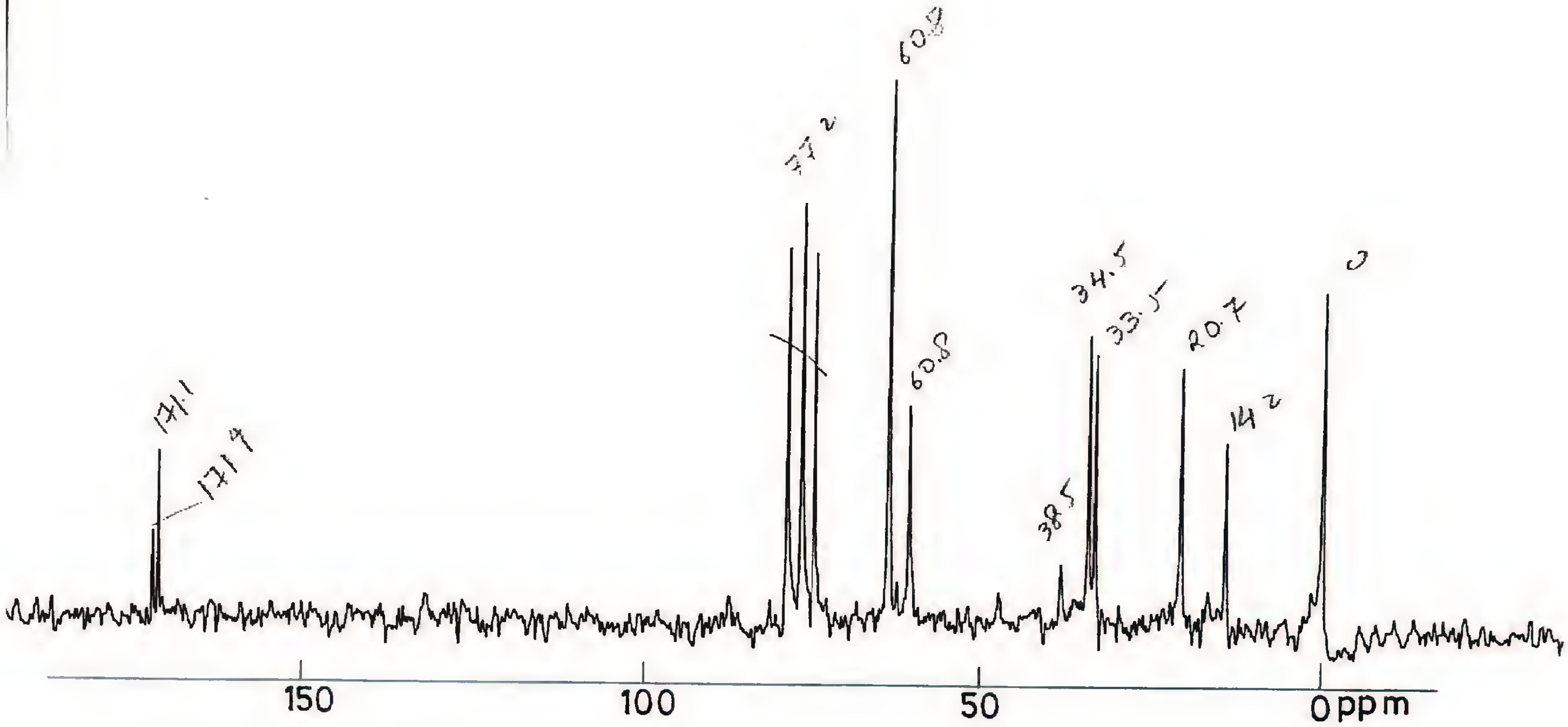
Spectrum P—2

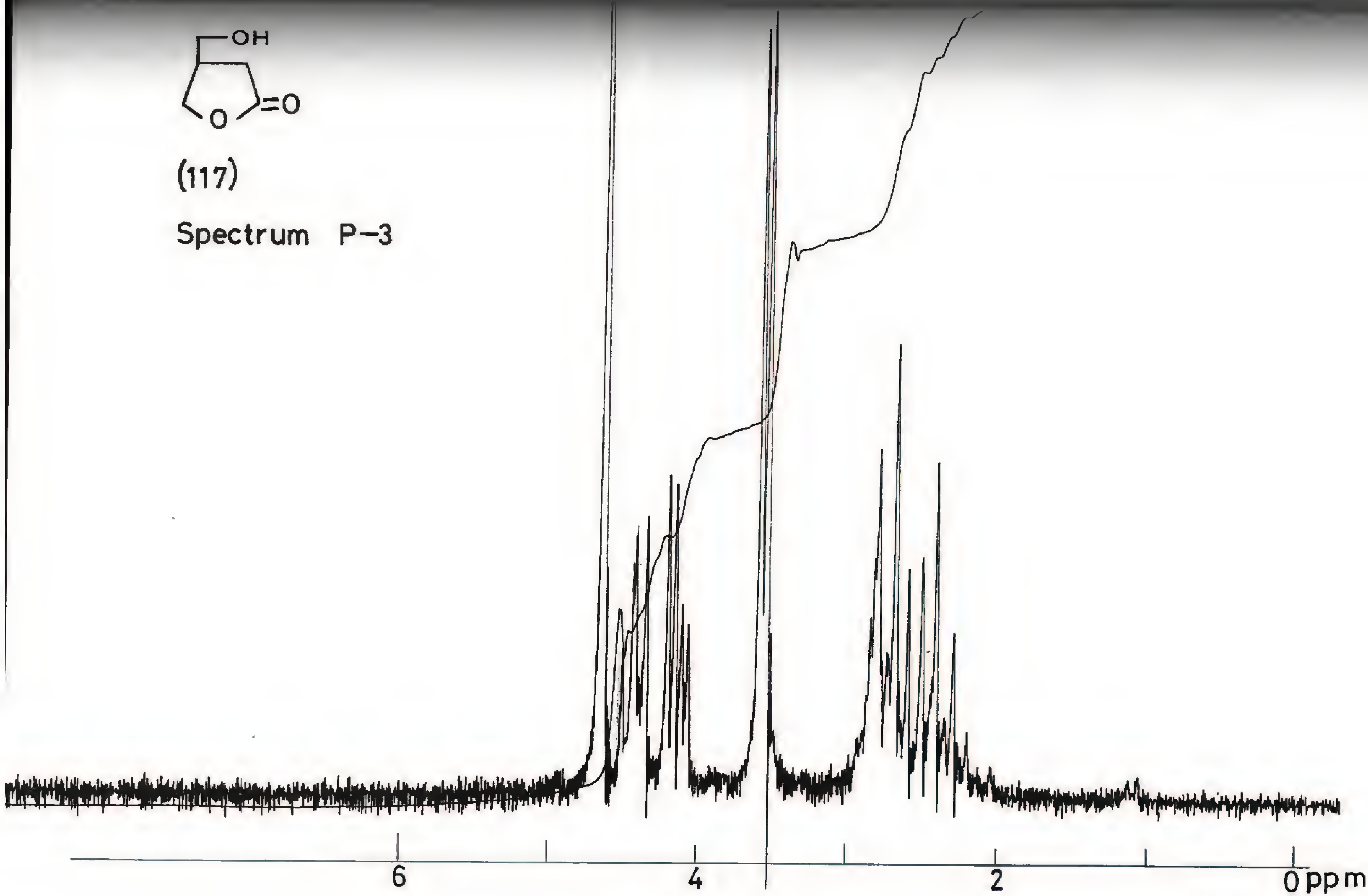


$CH_3CO_2CH_2CHCH_2O_2CCH_3$
$\qquad\qquad\quad|$
$\qquad\qquad CH_2CO_2CH_2CH_3$

(115)

Spectrum C-2



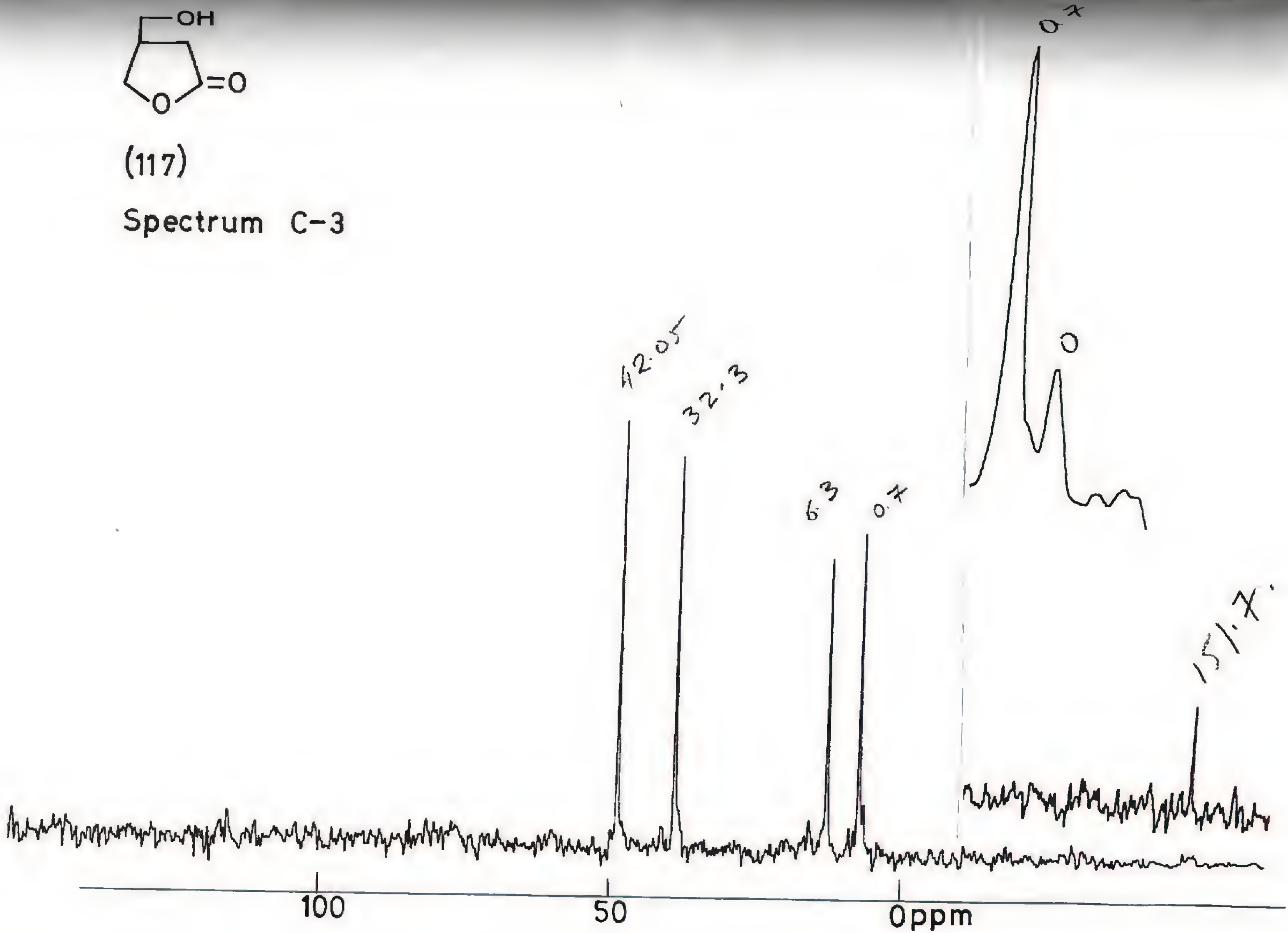


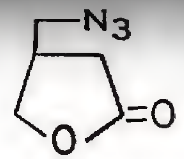
(117)

Spectrum P-3

(117)

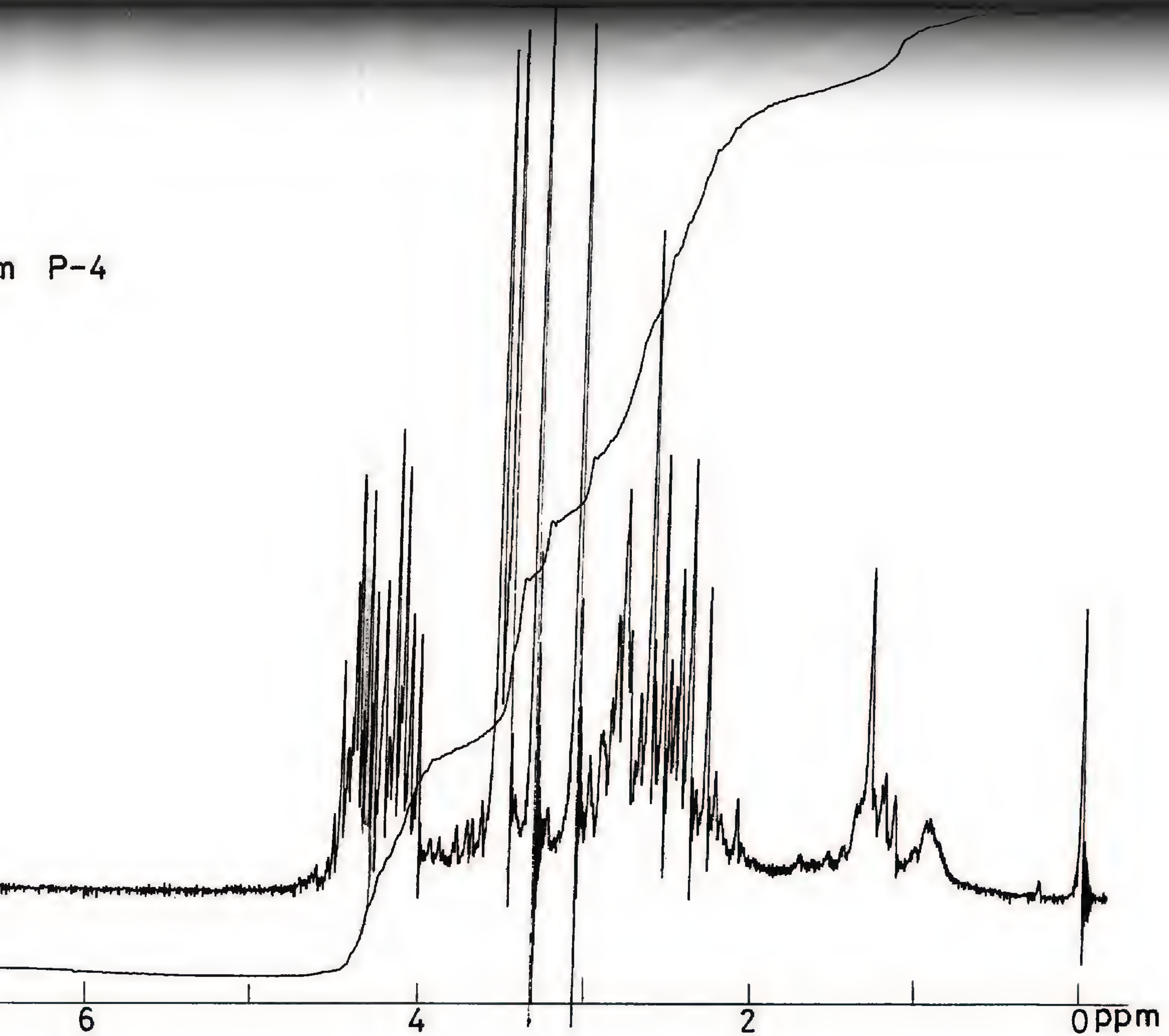
Spectrum C-3

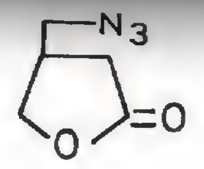




(119)

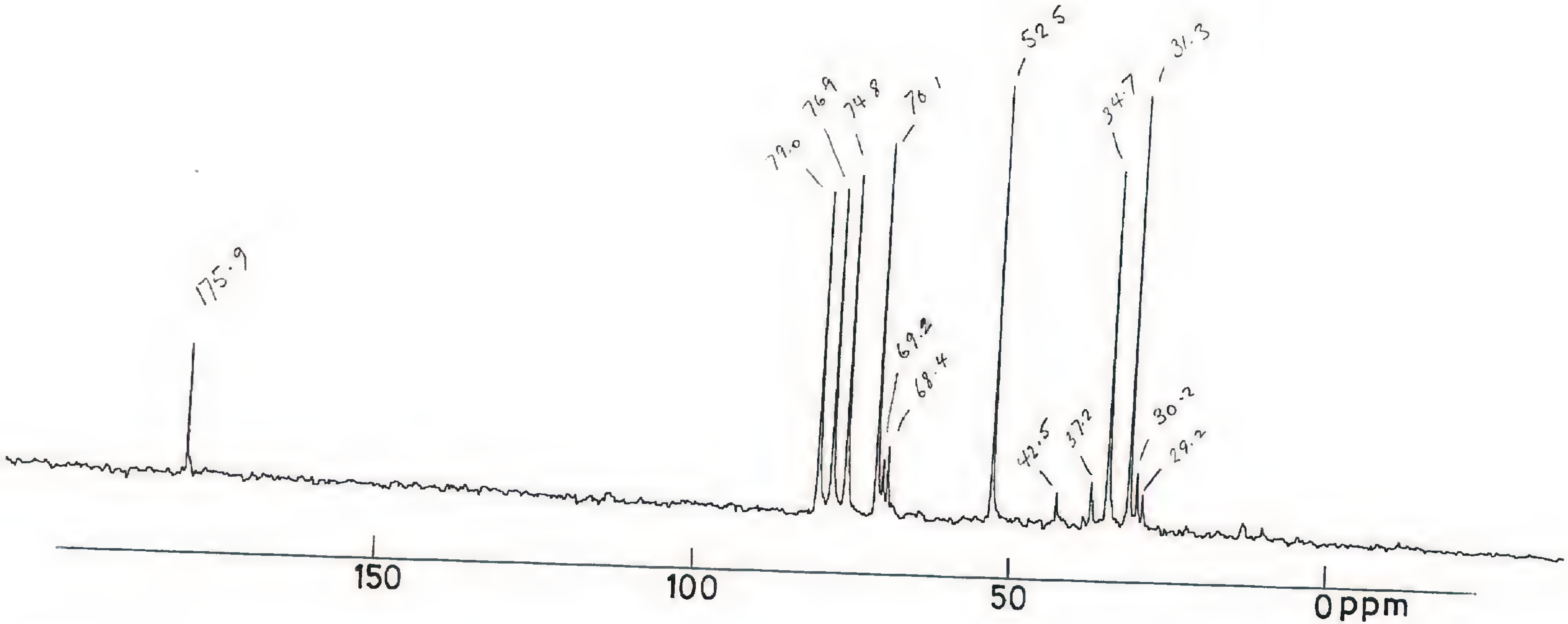
Spectrum P-4

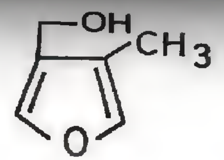




(119)

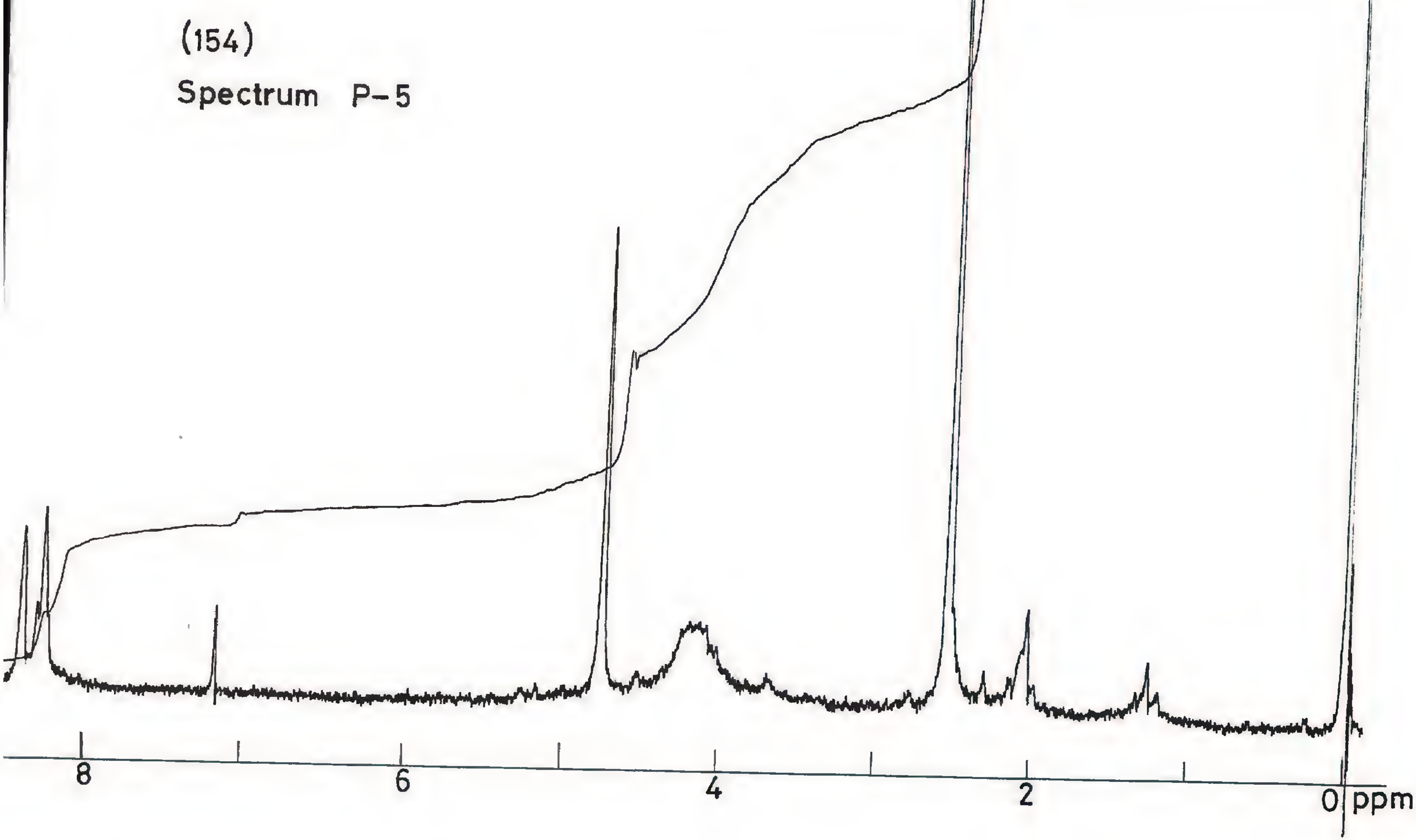
Spectrum C-4

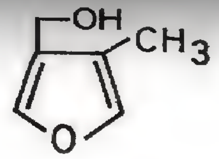




(154)

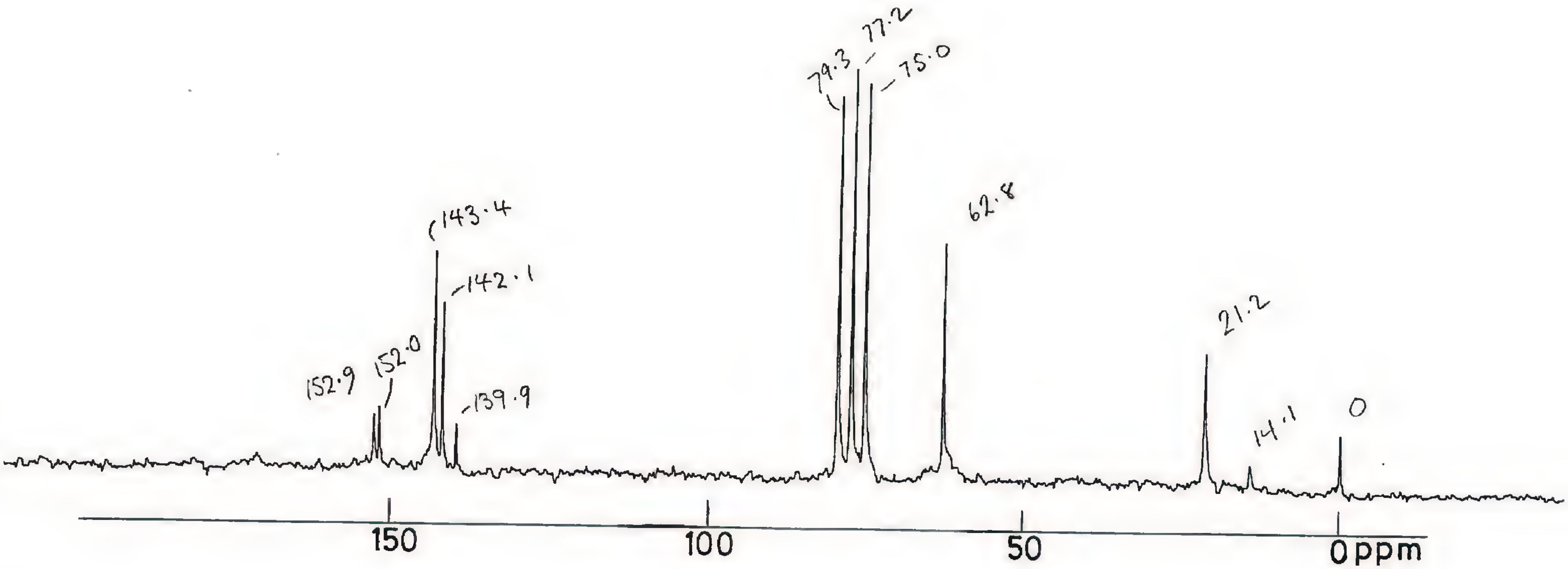
Spectrum P-5

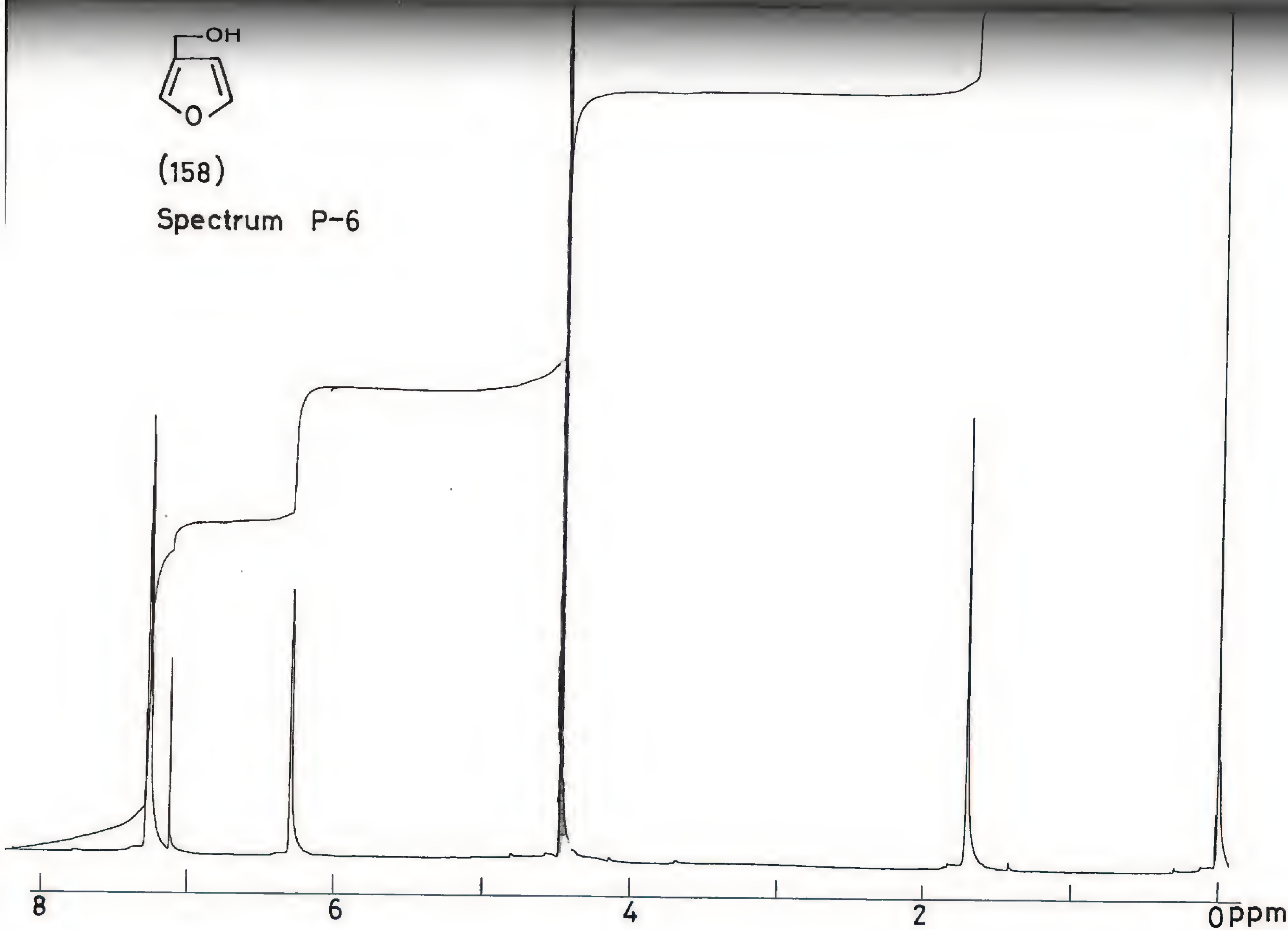




(154)

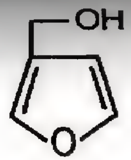
Spectrum C-5





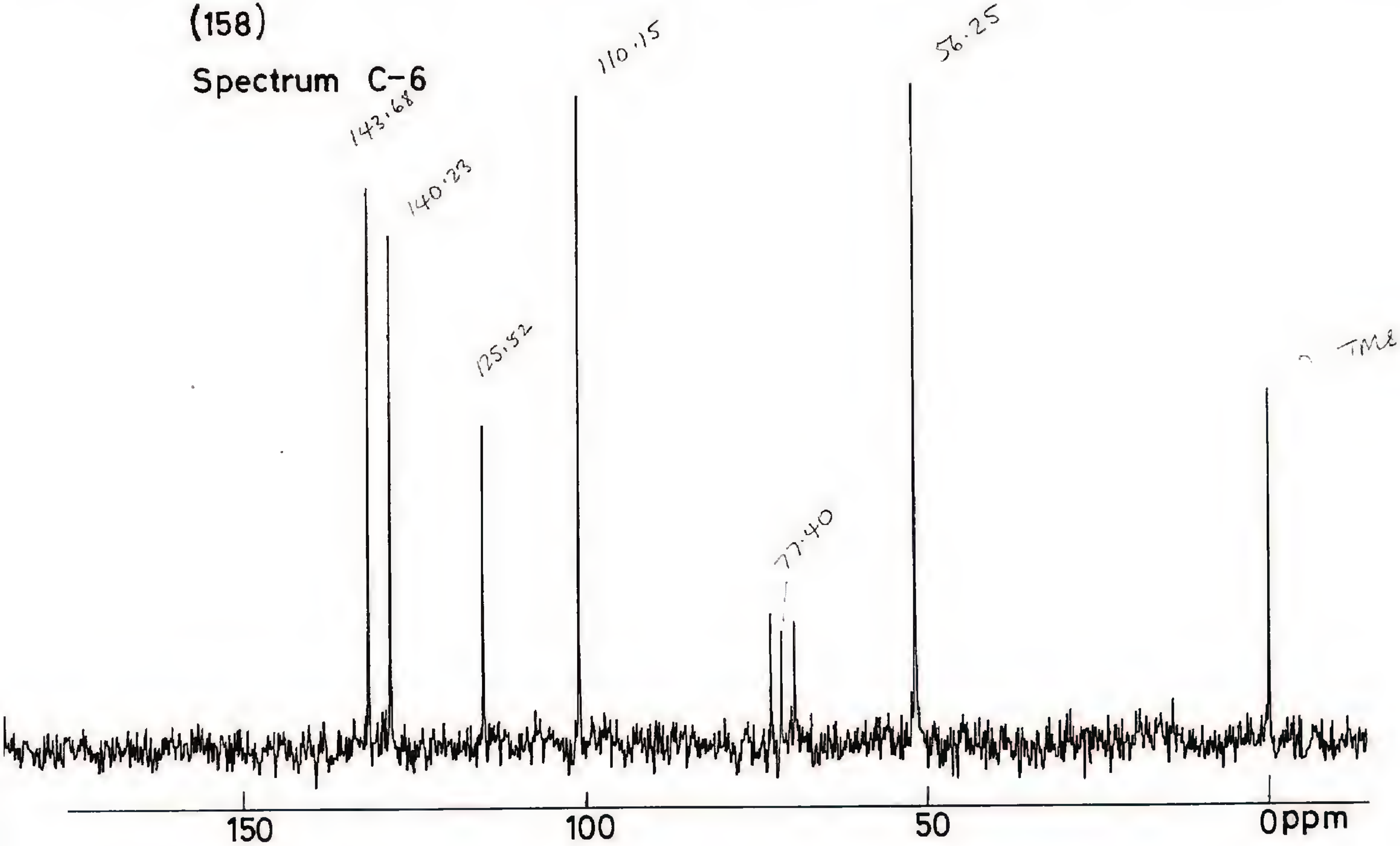
(158)

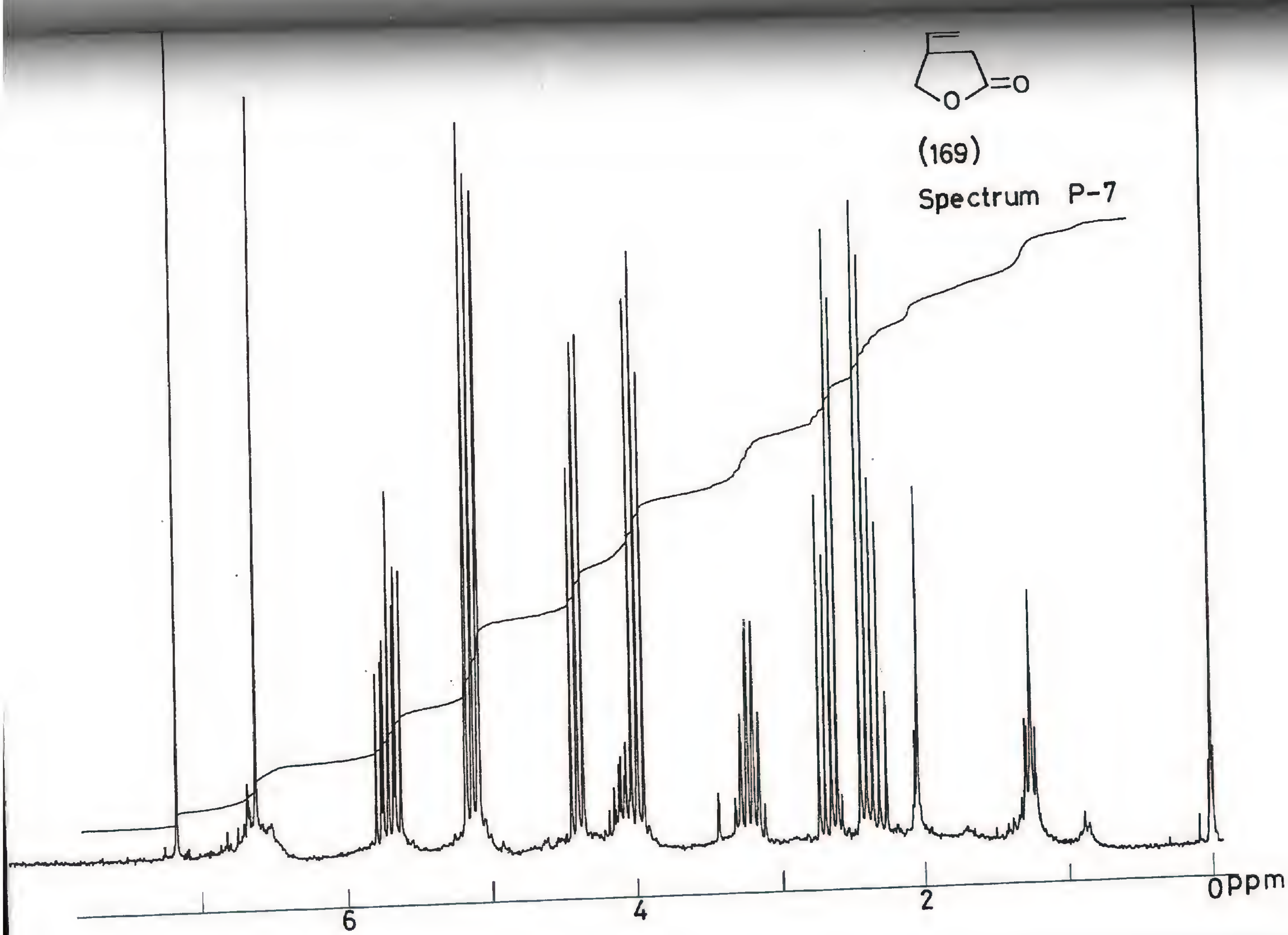
Spectrum P-6



(158)

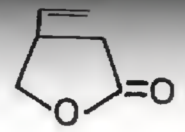
Spectrum C-6





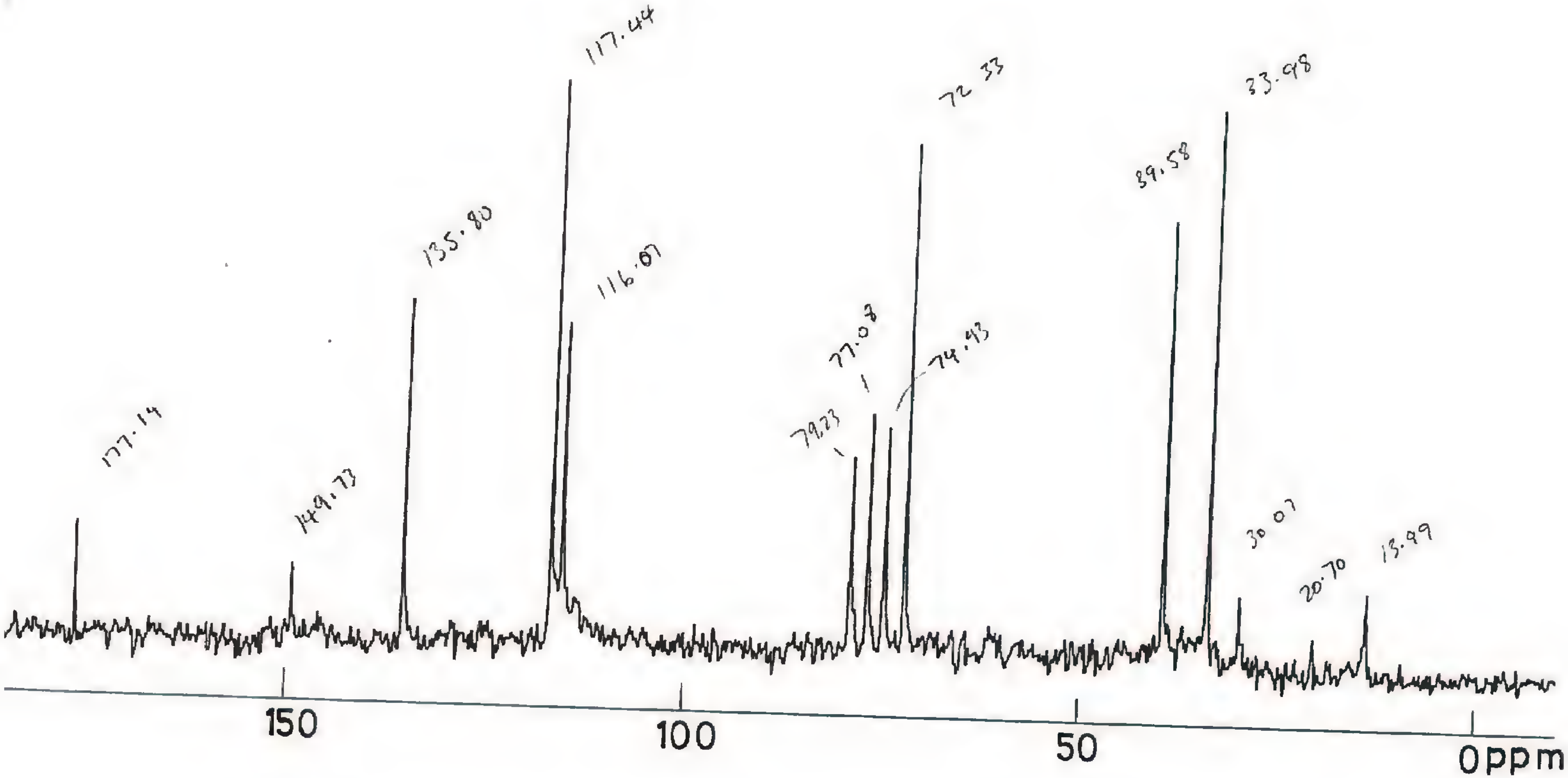
(169)

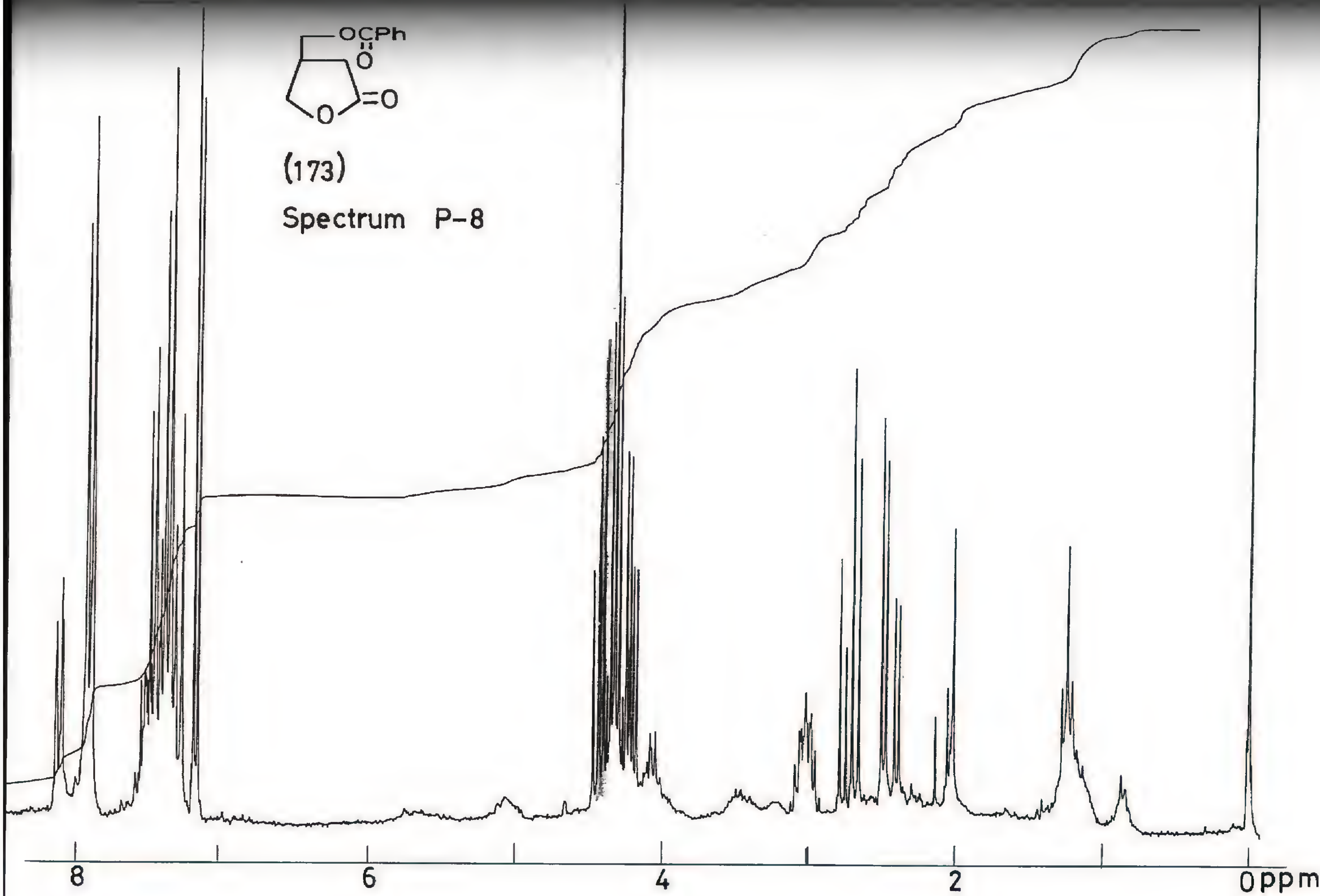
Spectrum P-7



(169)

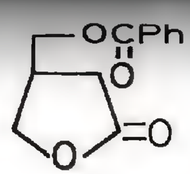
Spectrum C–7





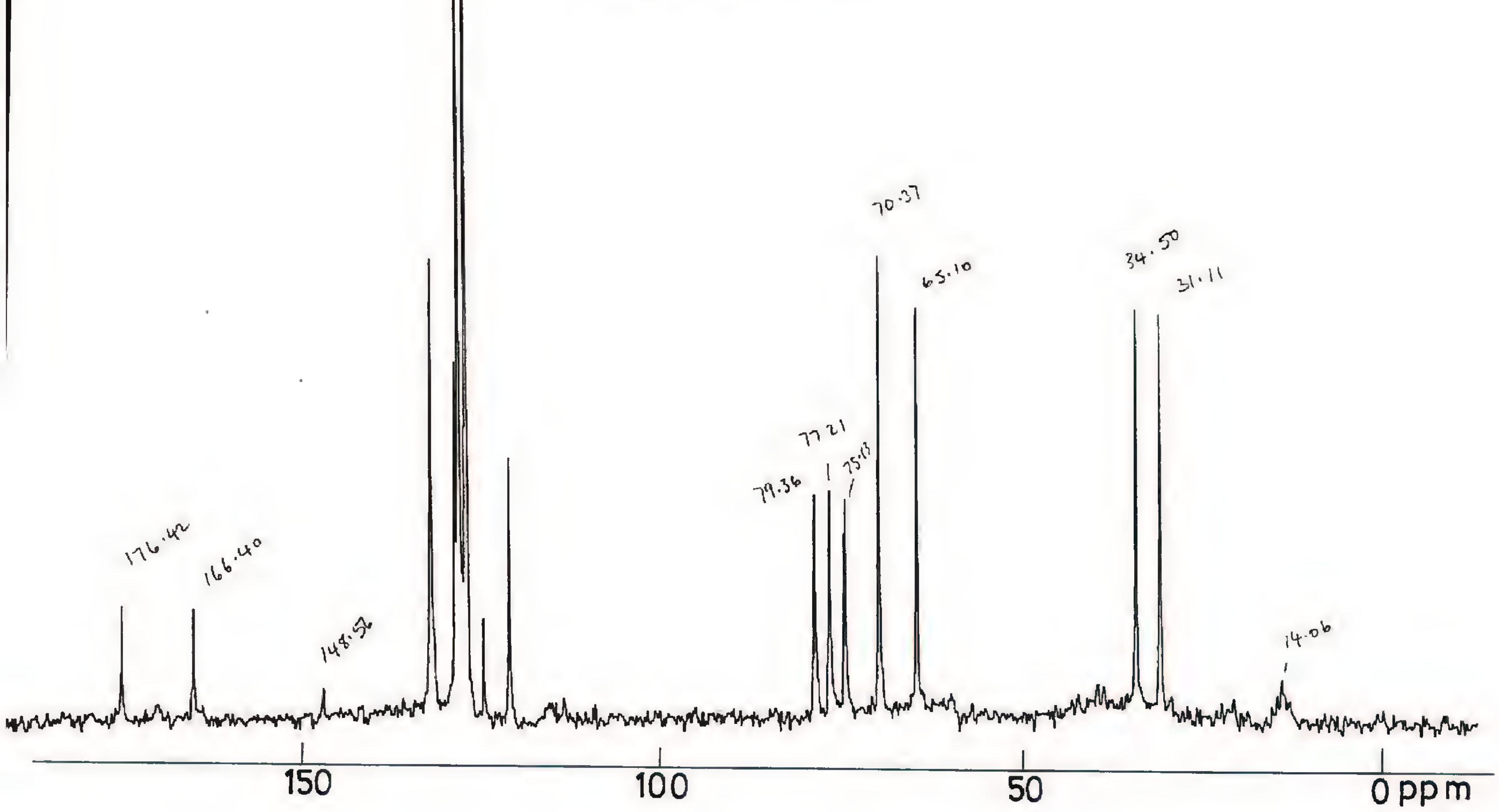
(173)

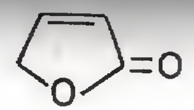
Spectrum P-8



(173)

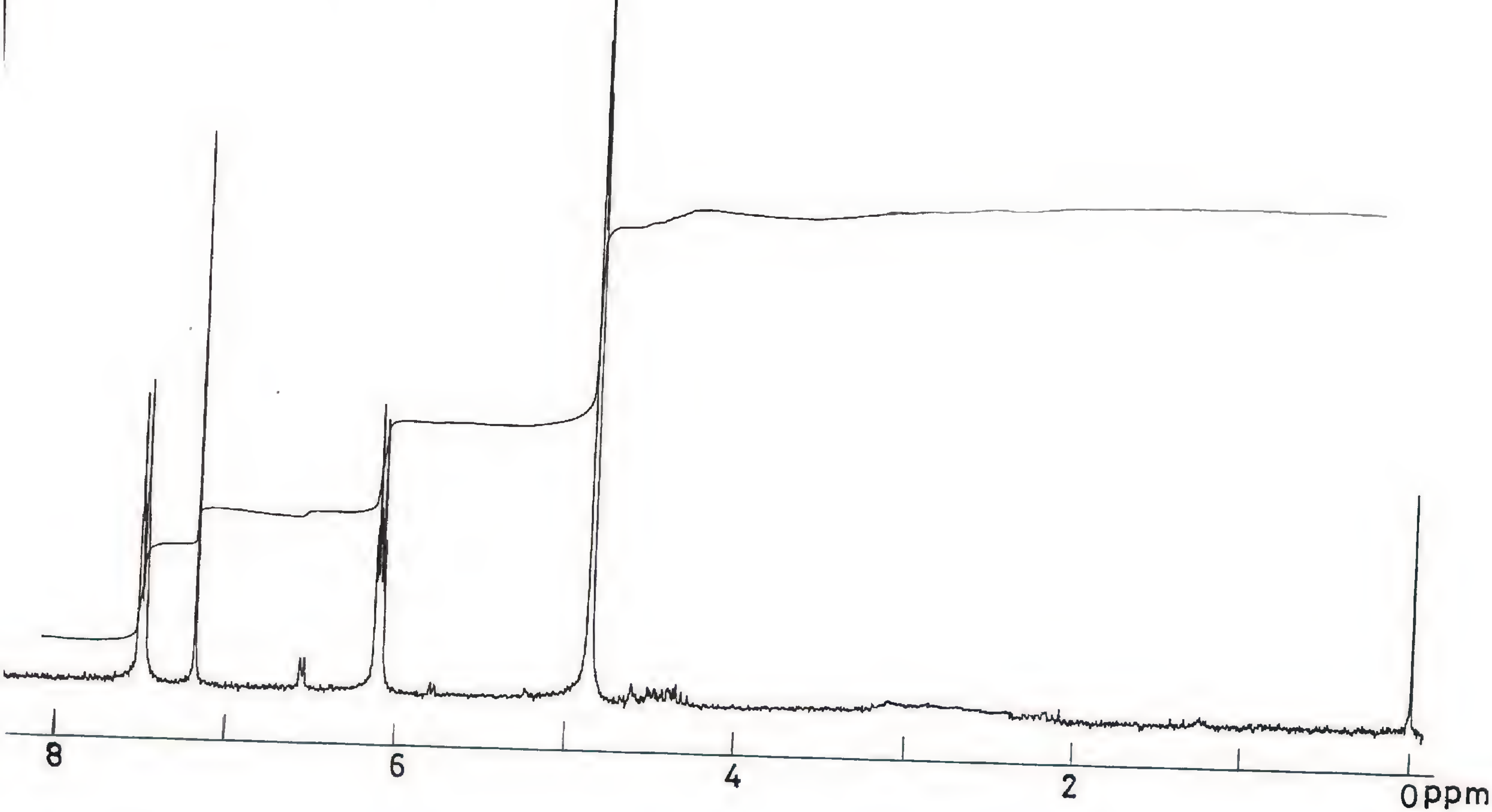
Spectrum C-8

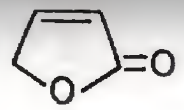




(181)

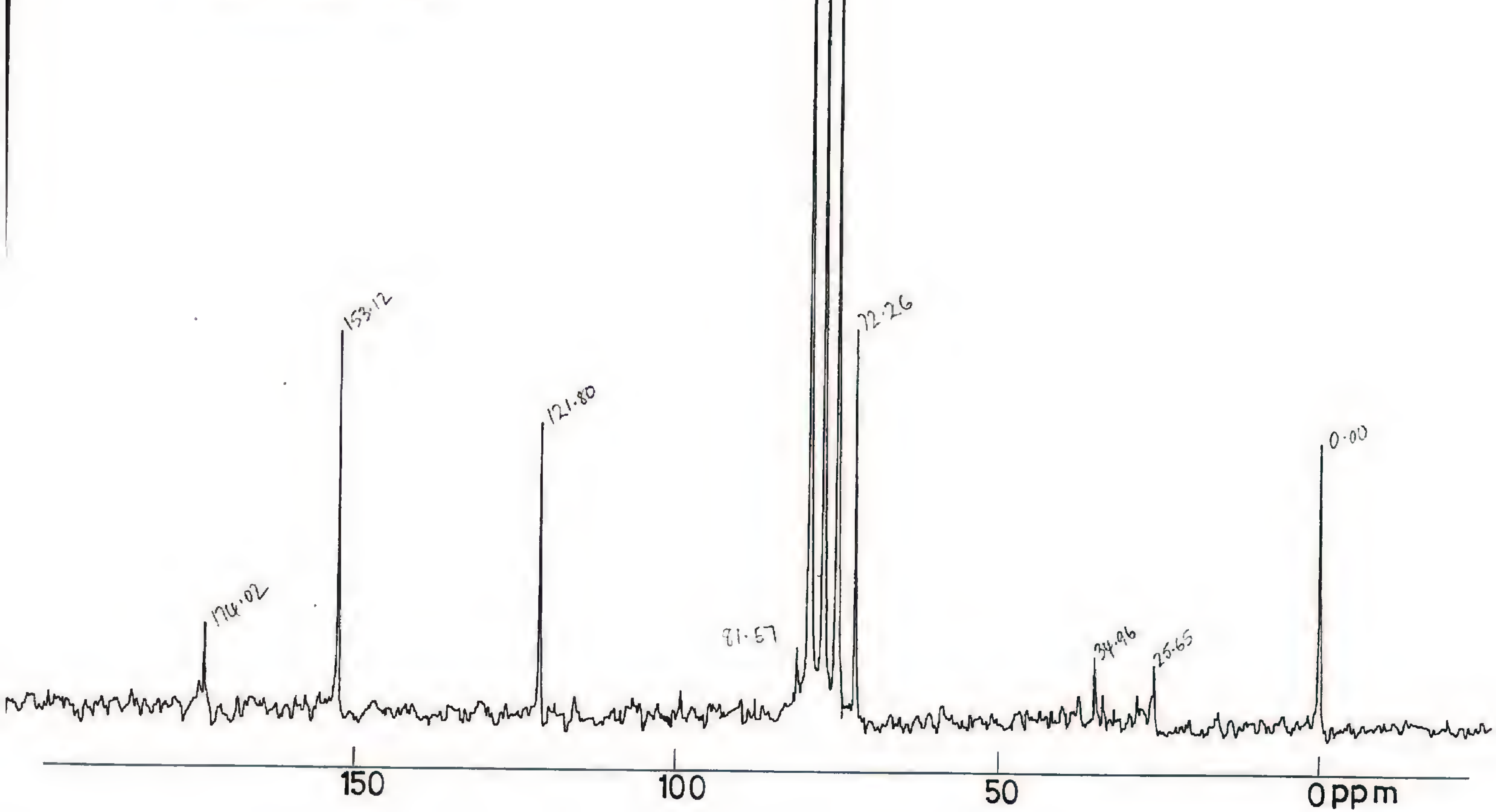
Spectrum P-9

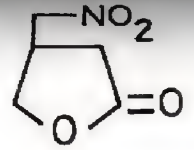




(181)

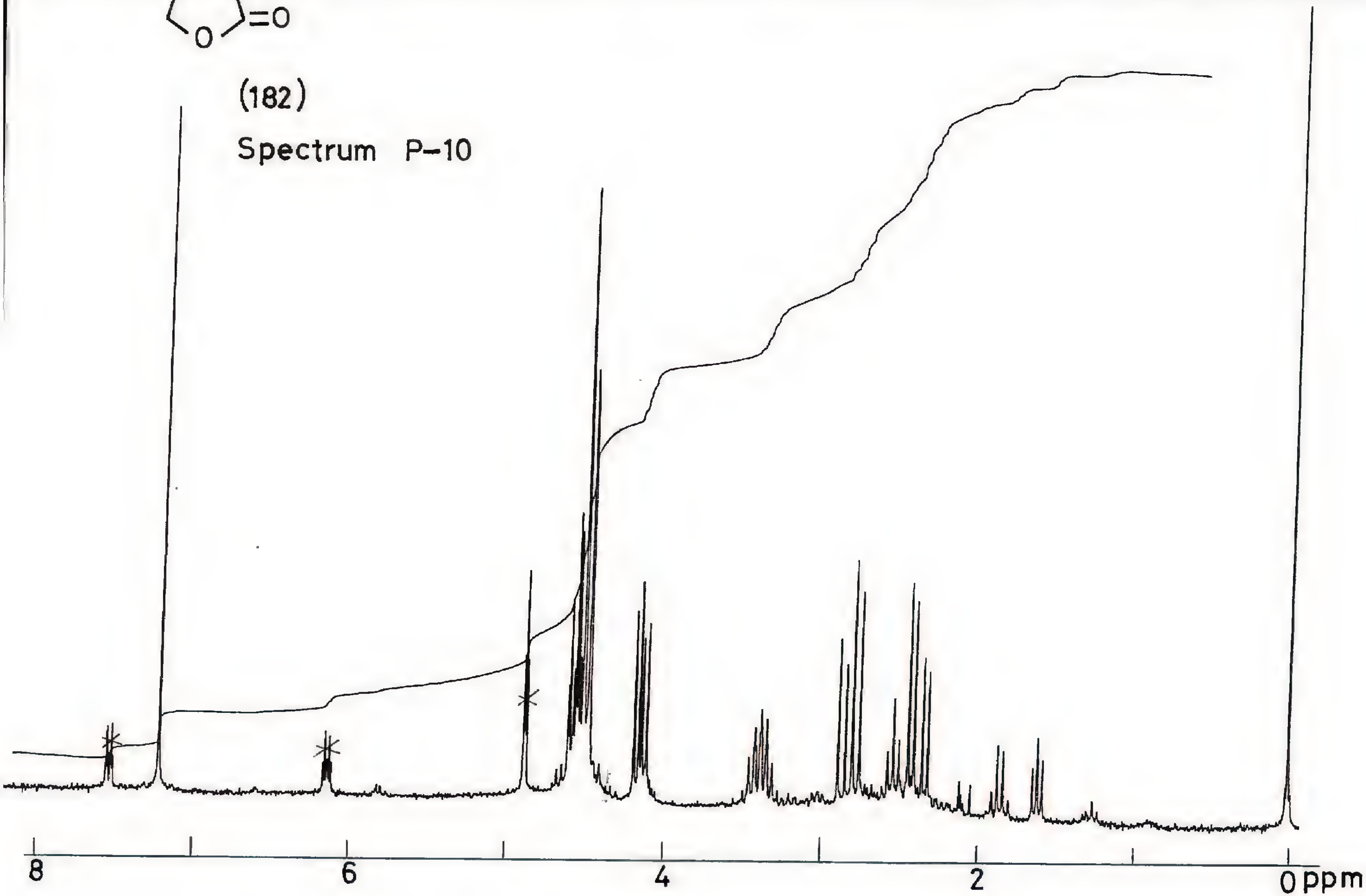
Spectrum C-9

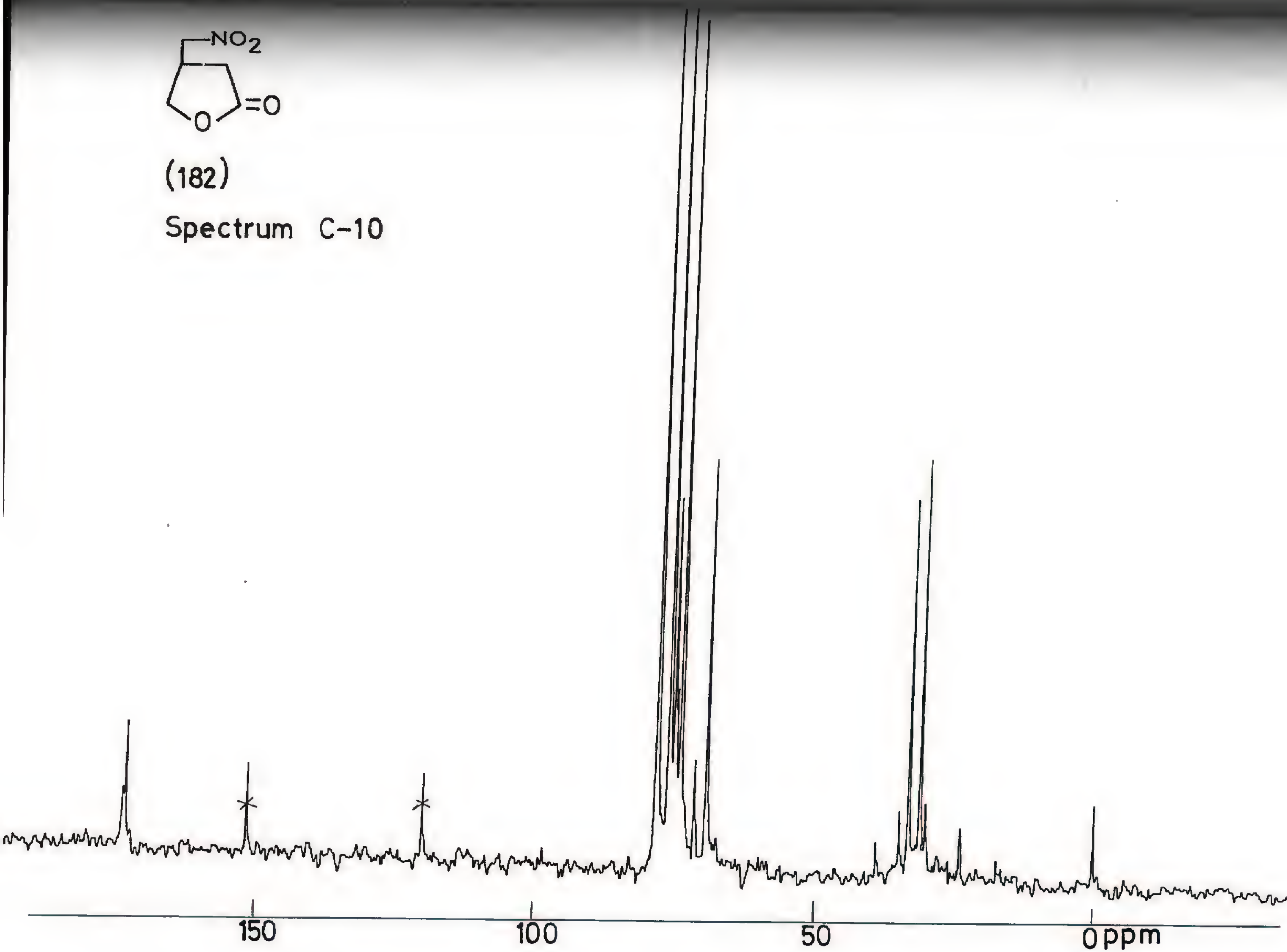




(182)

Spectrum P–10





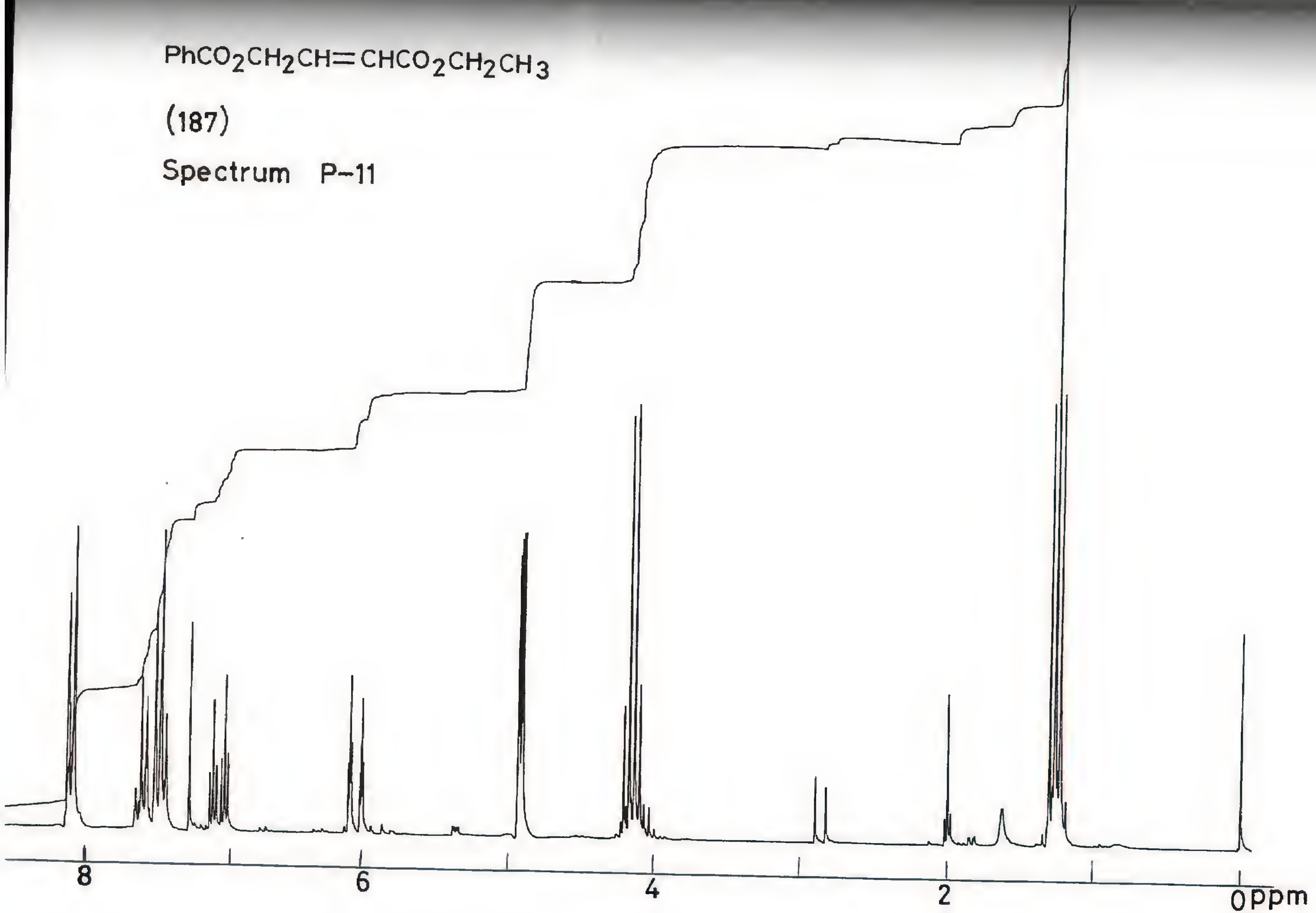
(182)

Spectrum C-10

$PhCO_2CH_2CH{=}CHCO_2CH_2CH_3$

(187)

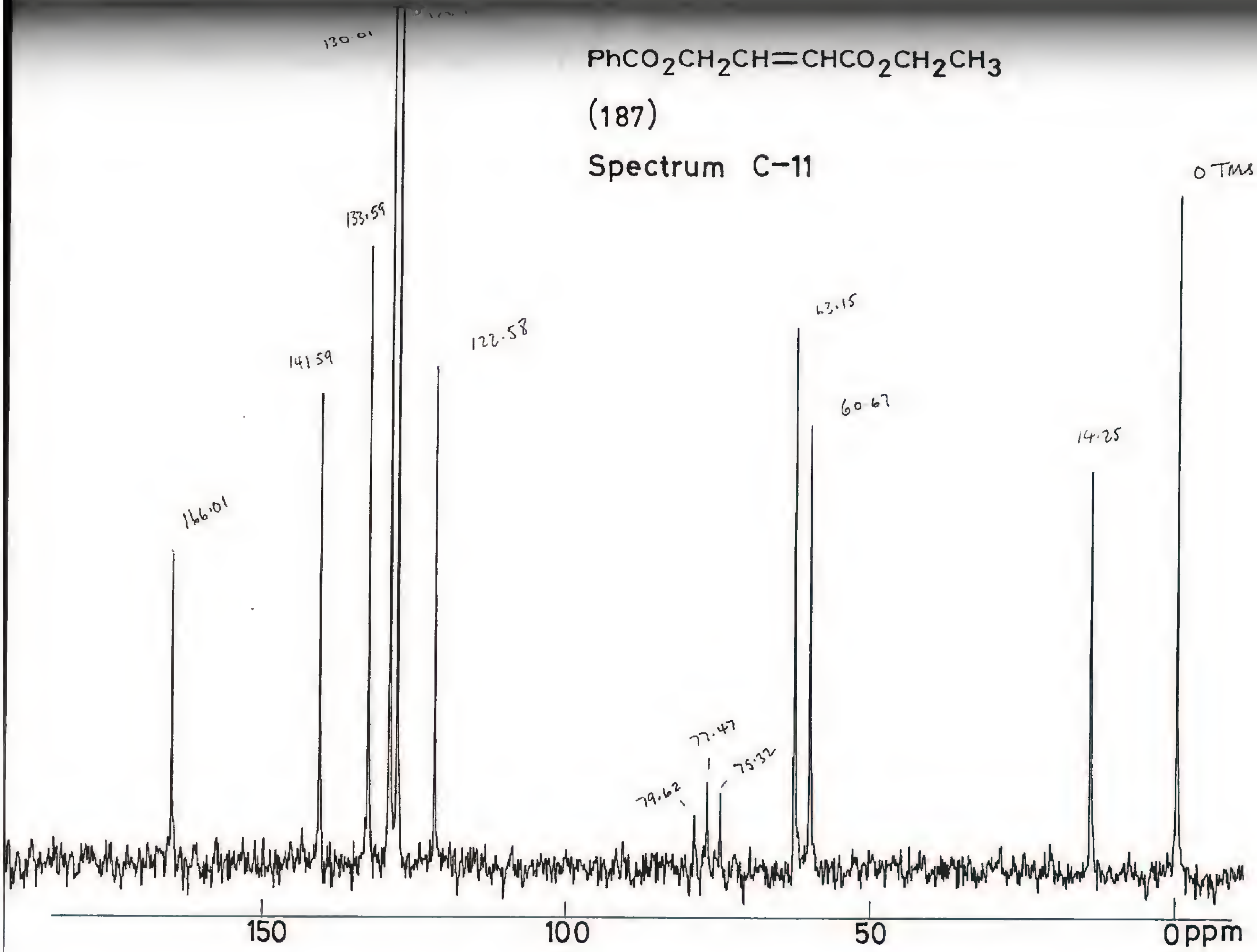
Spectrum P-11



$PhCO_2CH_2CH{=}CHCO_2CH_2CH_3$

(187)

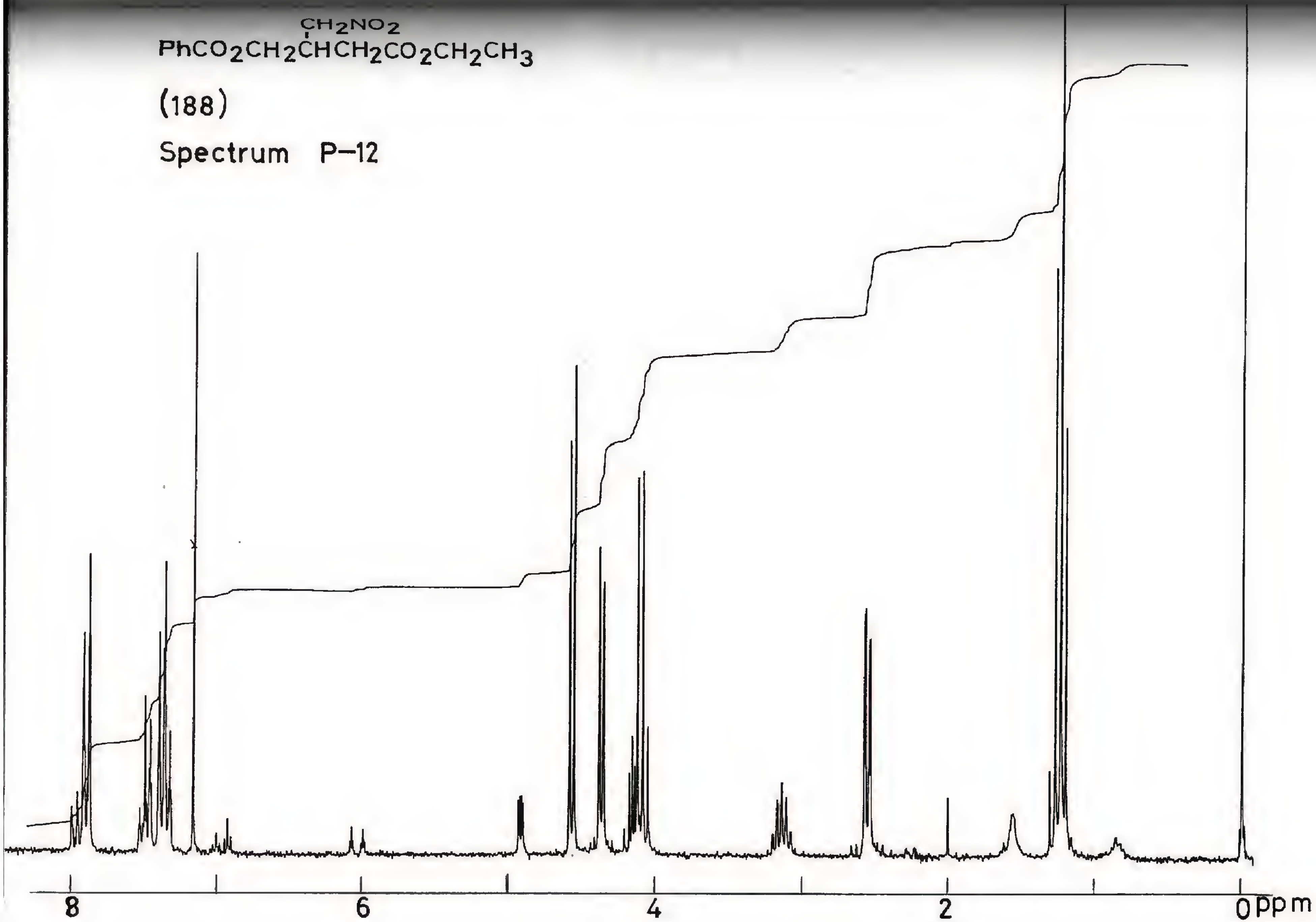
Spectrum C–11



$PhCO_2CH_2CH(CH_2NO_2)CH_2CO_2CH_2CH_3$

(188)

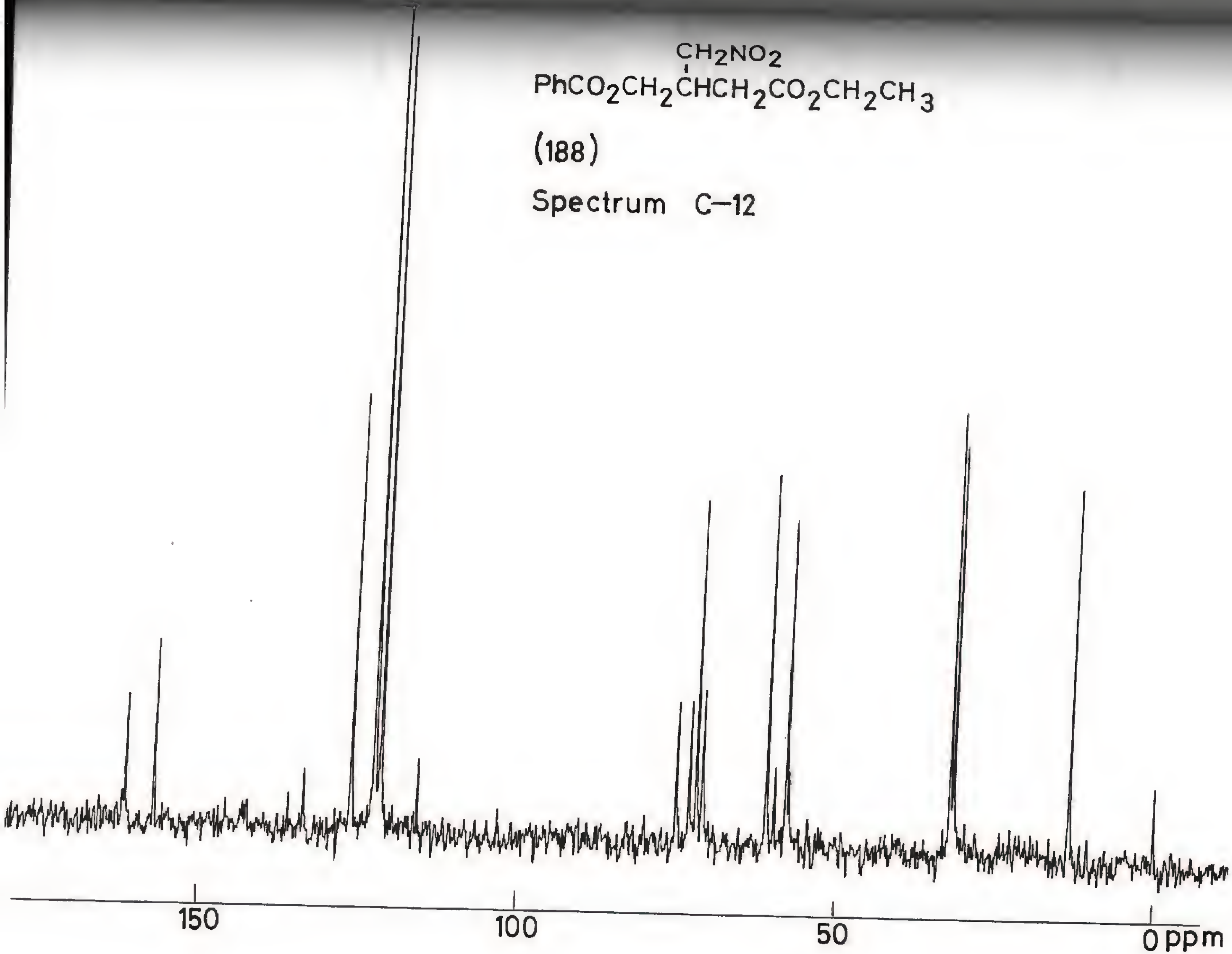
Spectrum P-12

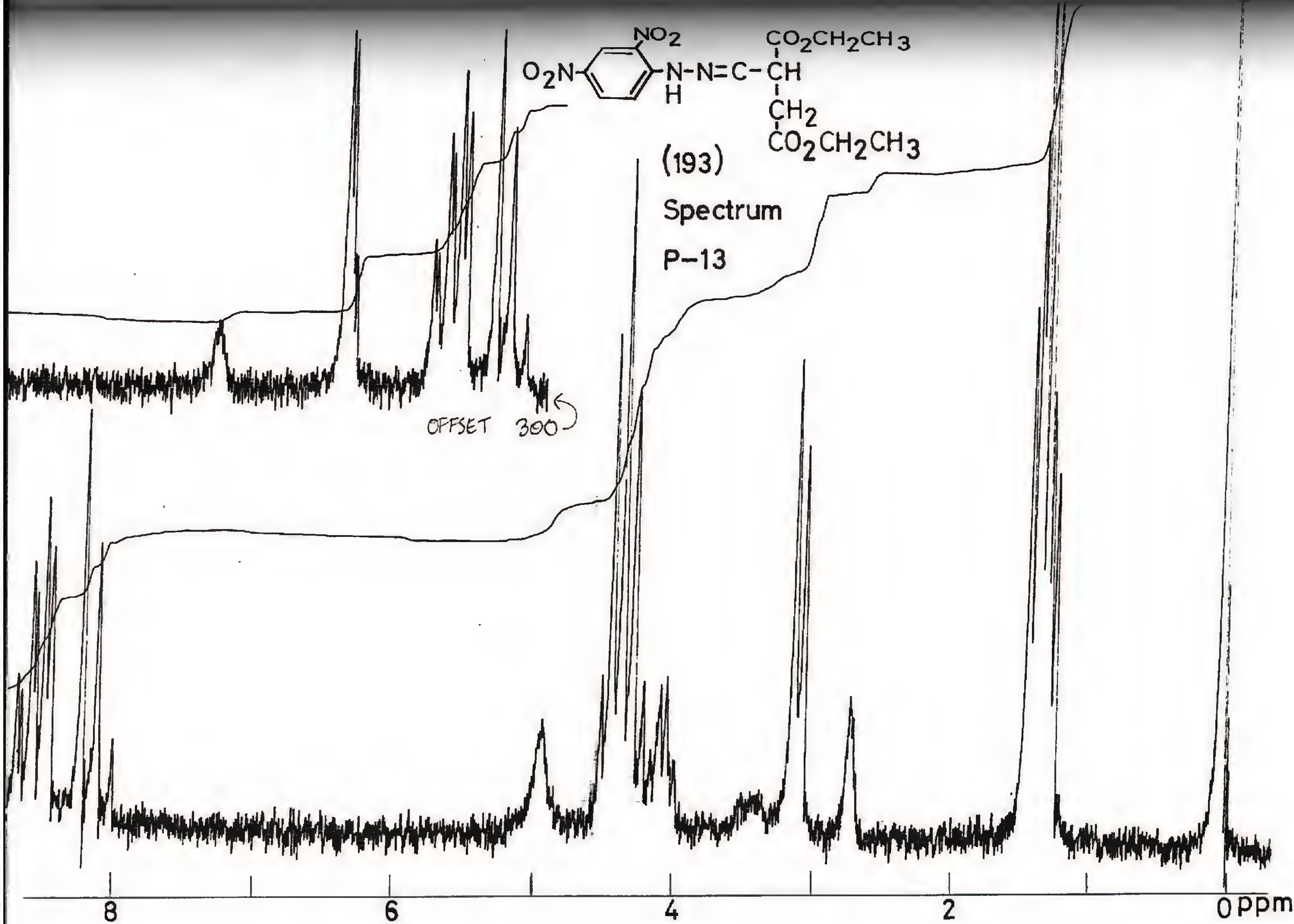


$$\begin{array}{c}\quad\quad CH_2NO_2\\ PhCO_2CH_2\overset{|}{C}HCH_2CO_2CH_2CH_3\end{array}$$

(188)

Spectrum C–12

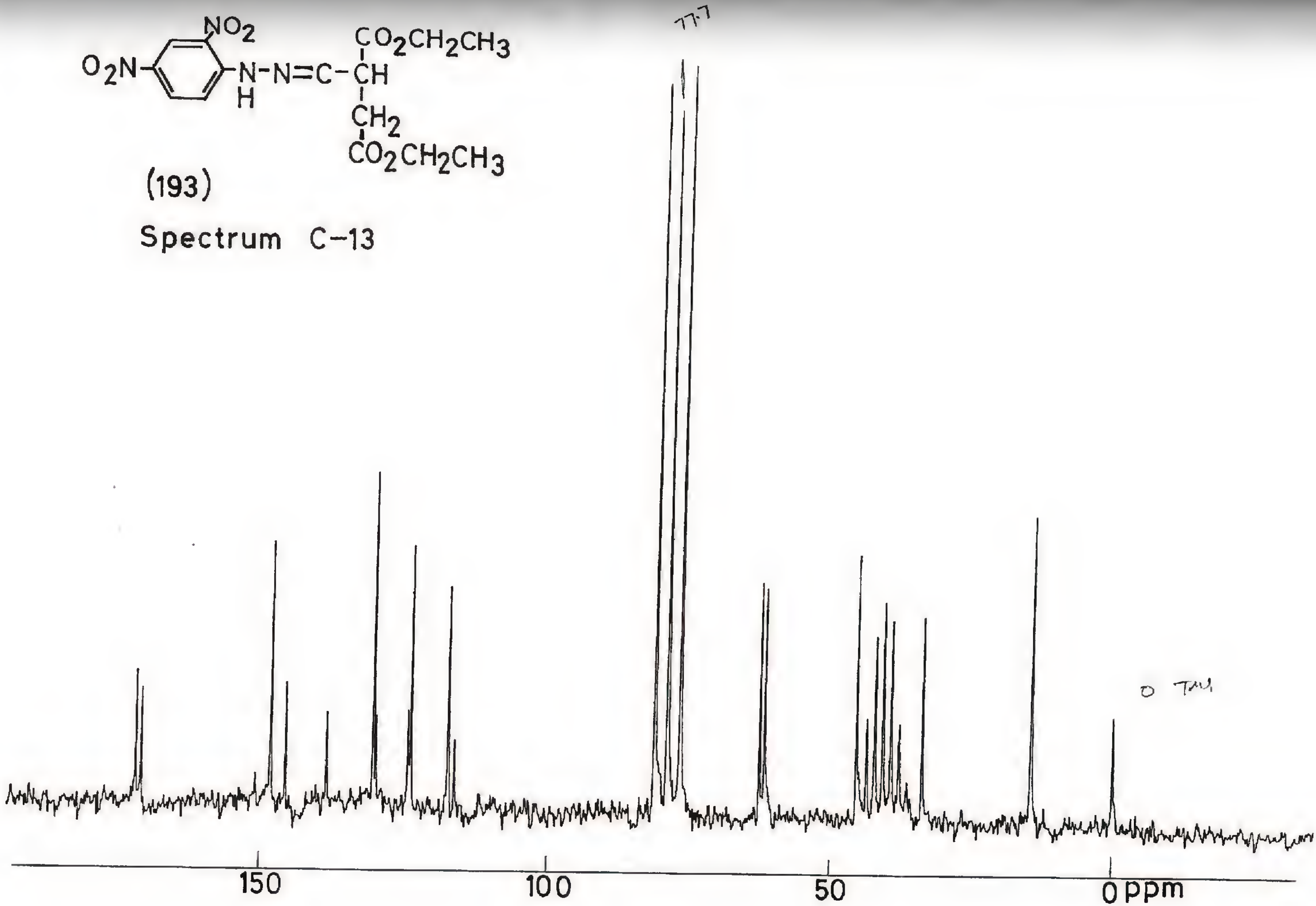




(193)

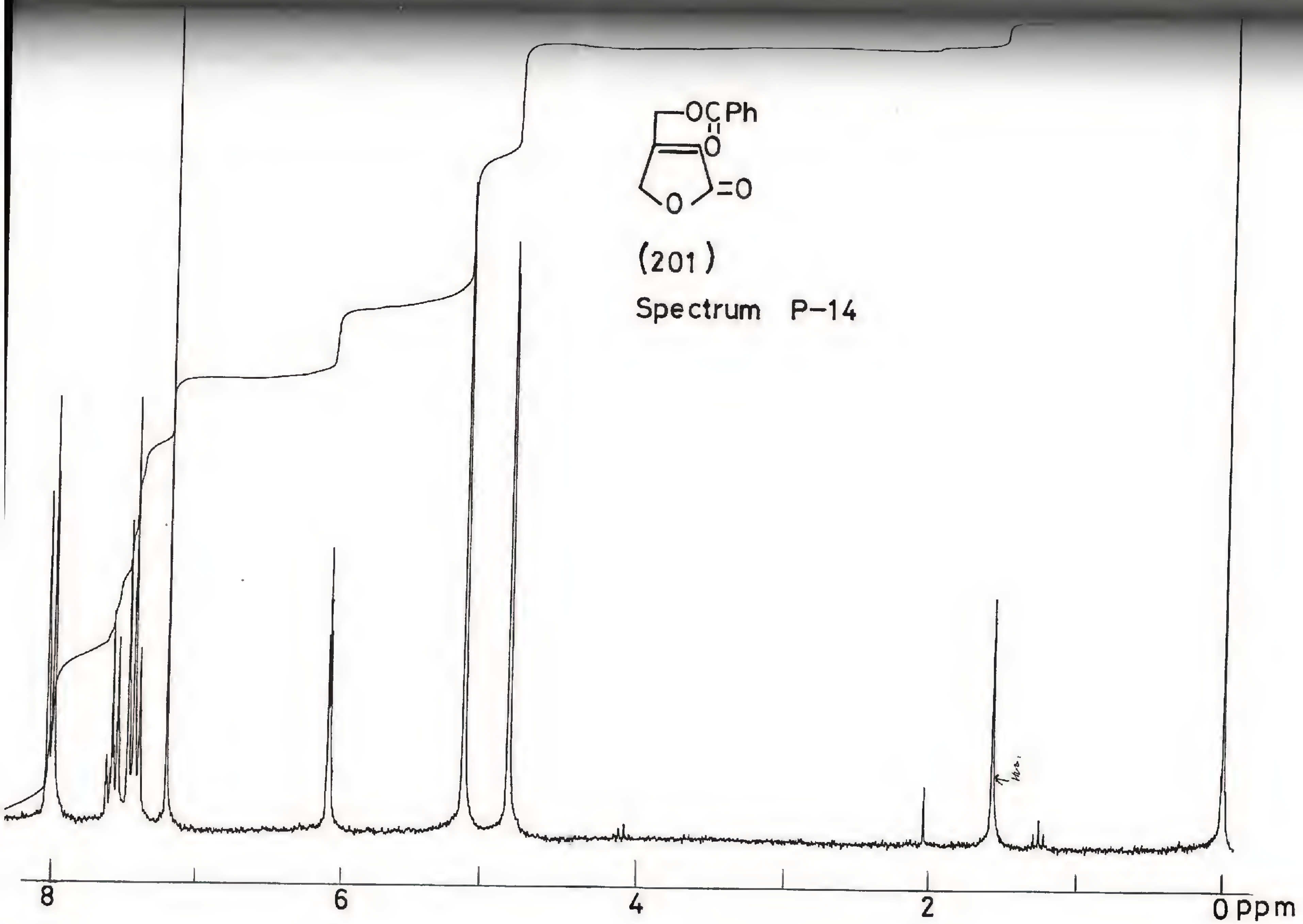
Spectrum

P–13



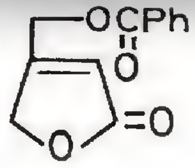
(193)

Spectrum C–13



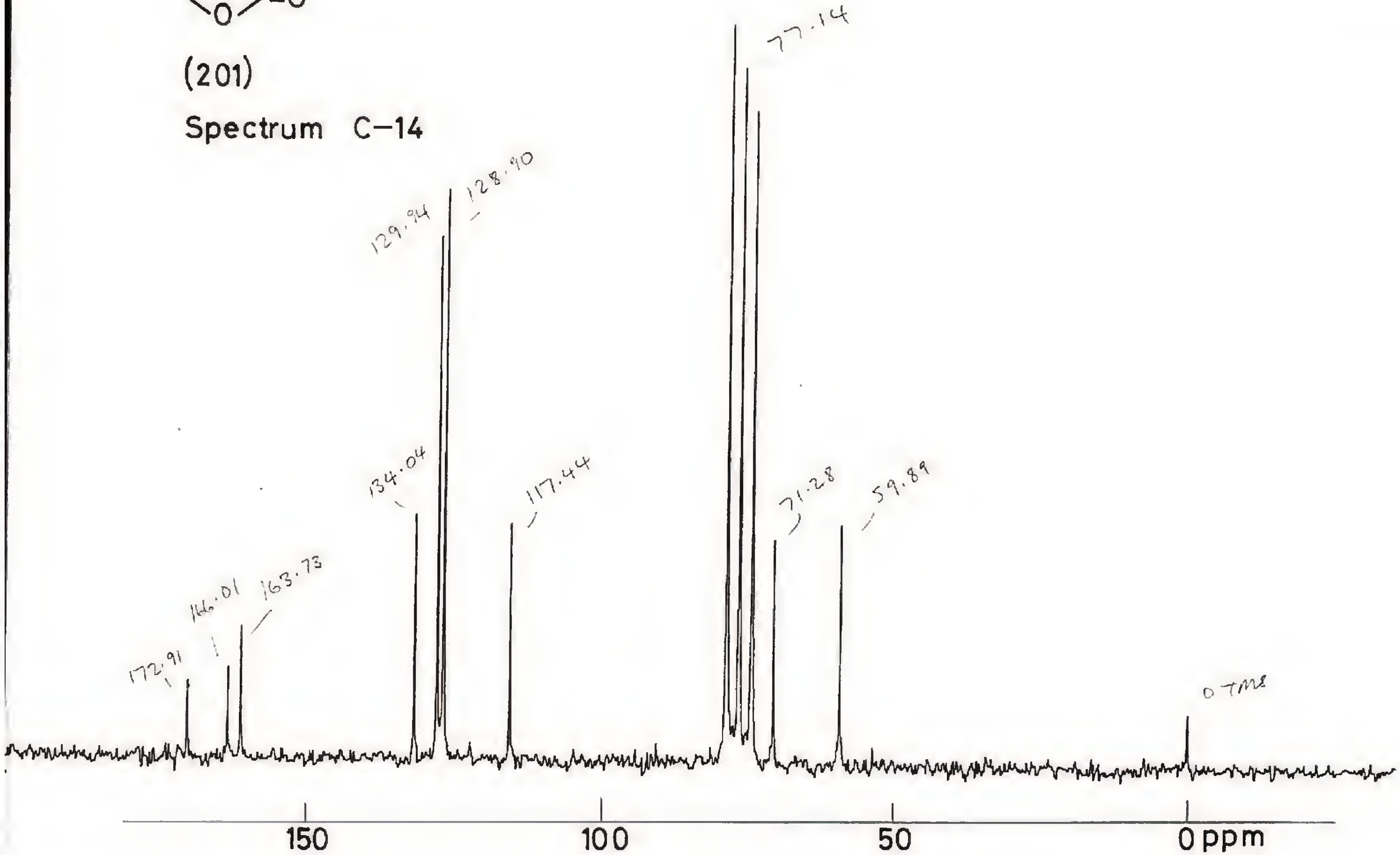
(201)

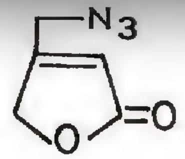
Spectrum P-14



(201)

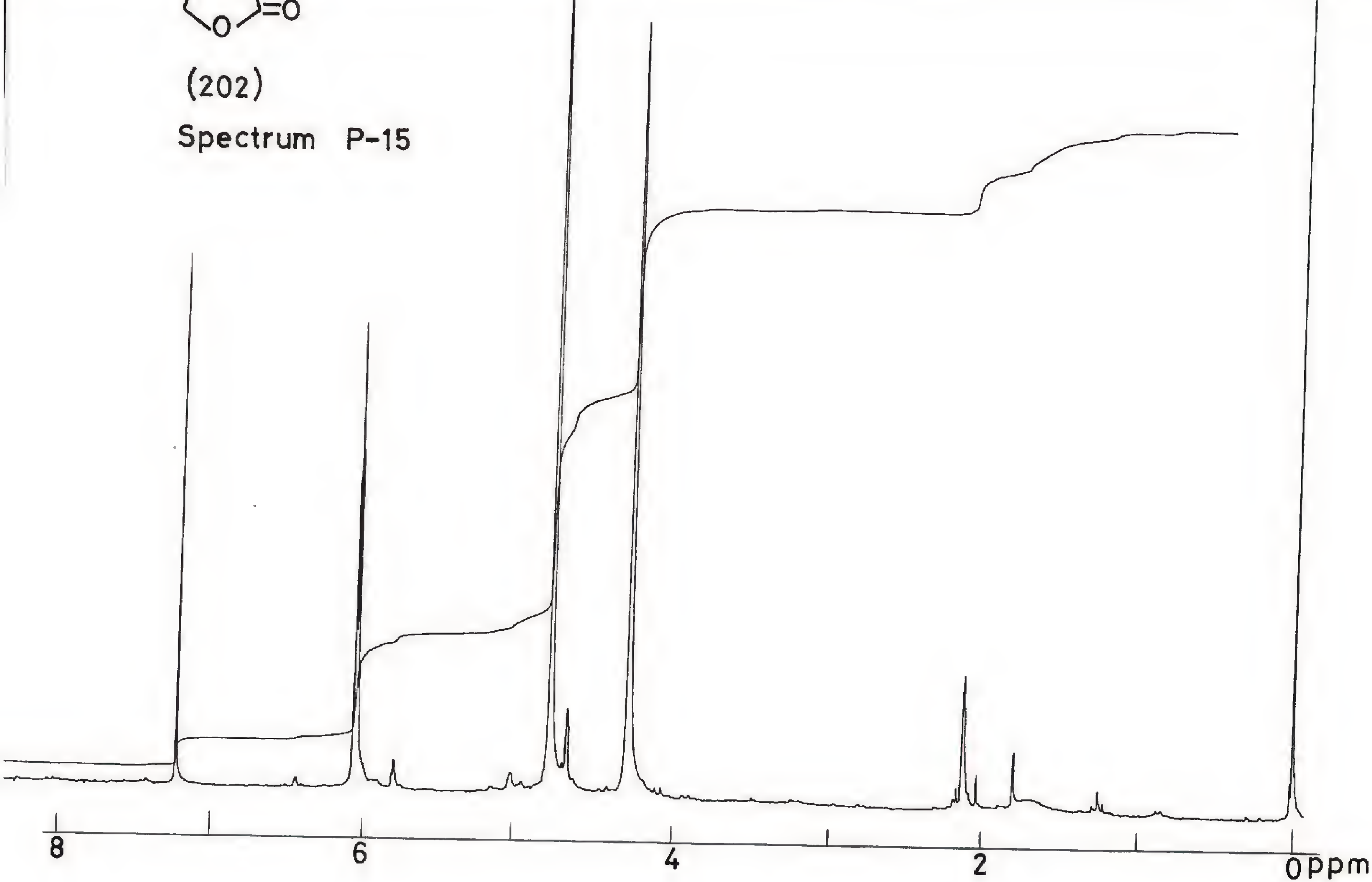
Spectrum C–14

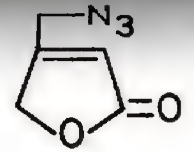




(202)

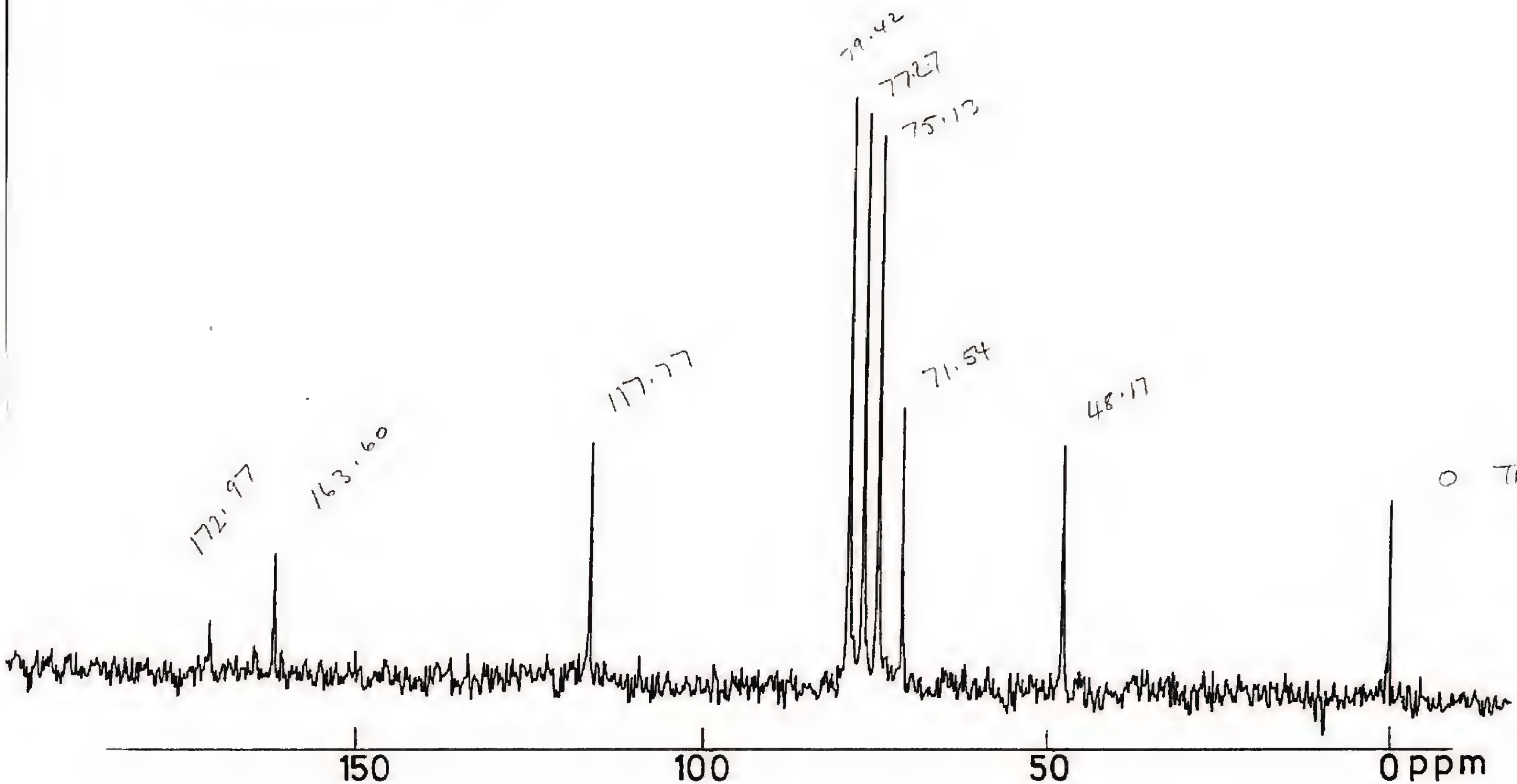
Spectrum P-15

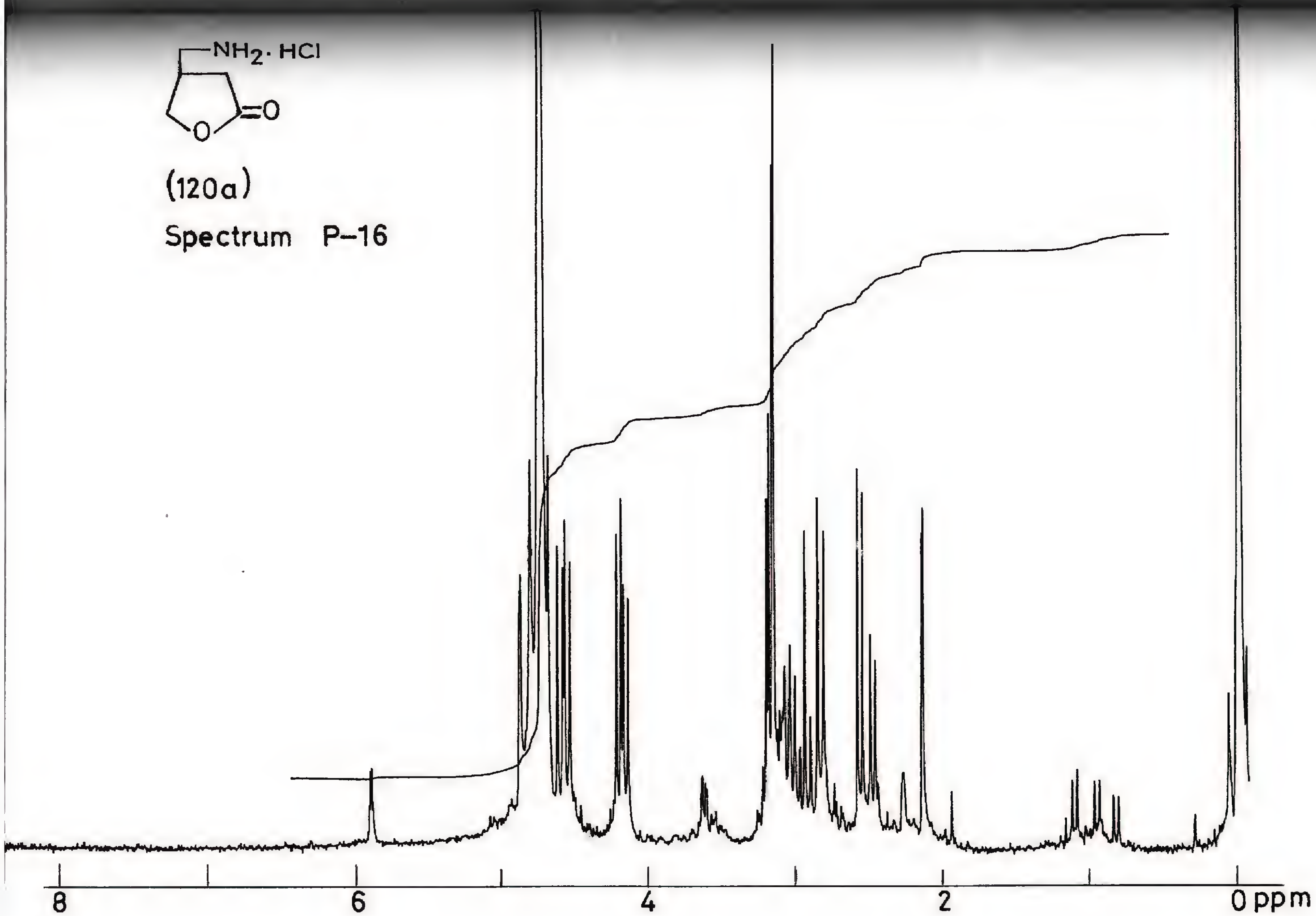




(202)

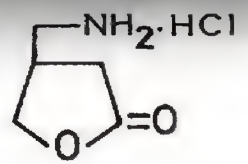
Spectrum C-15





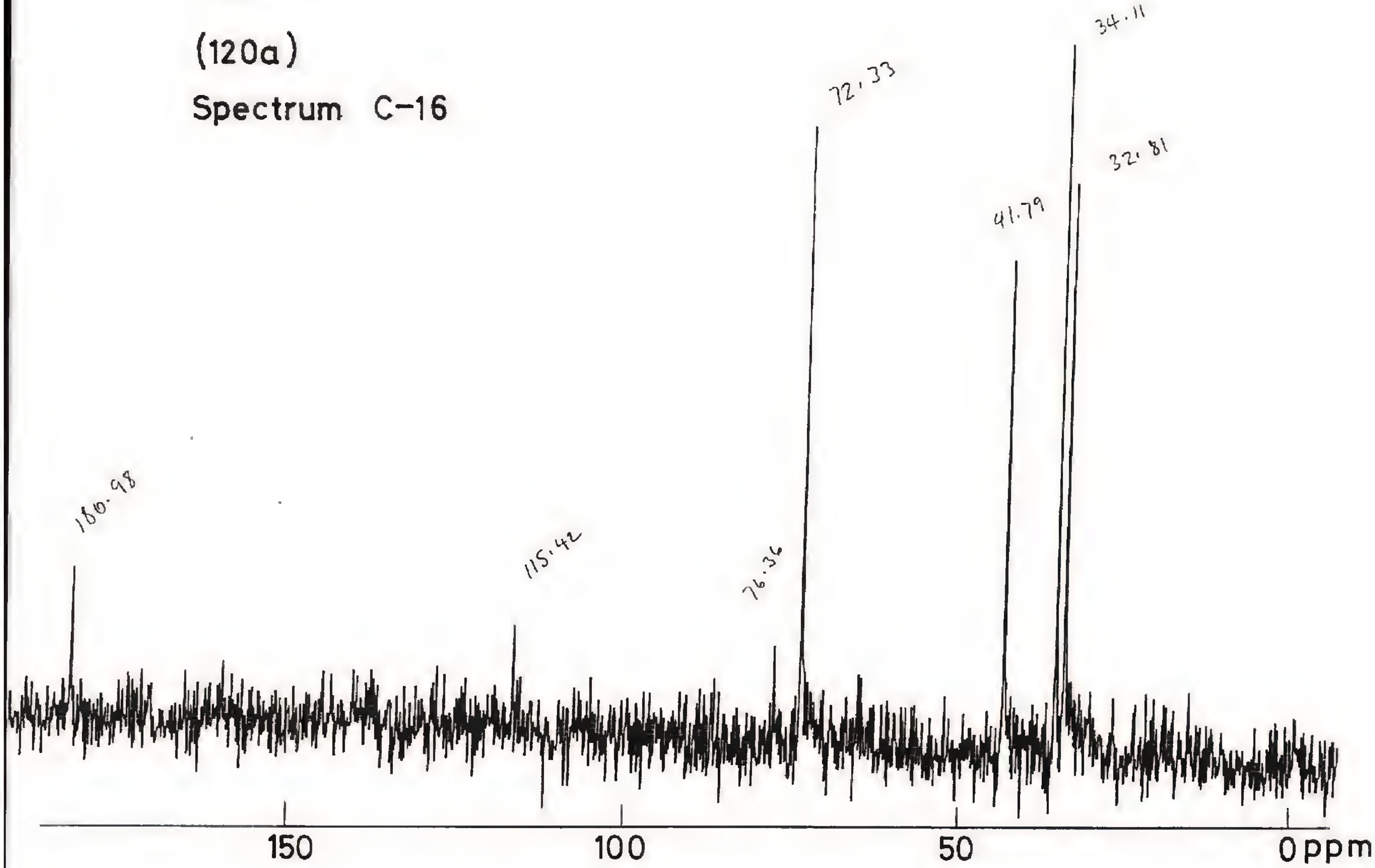
(120a)

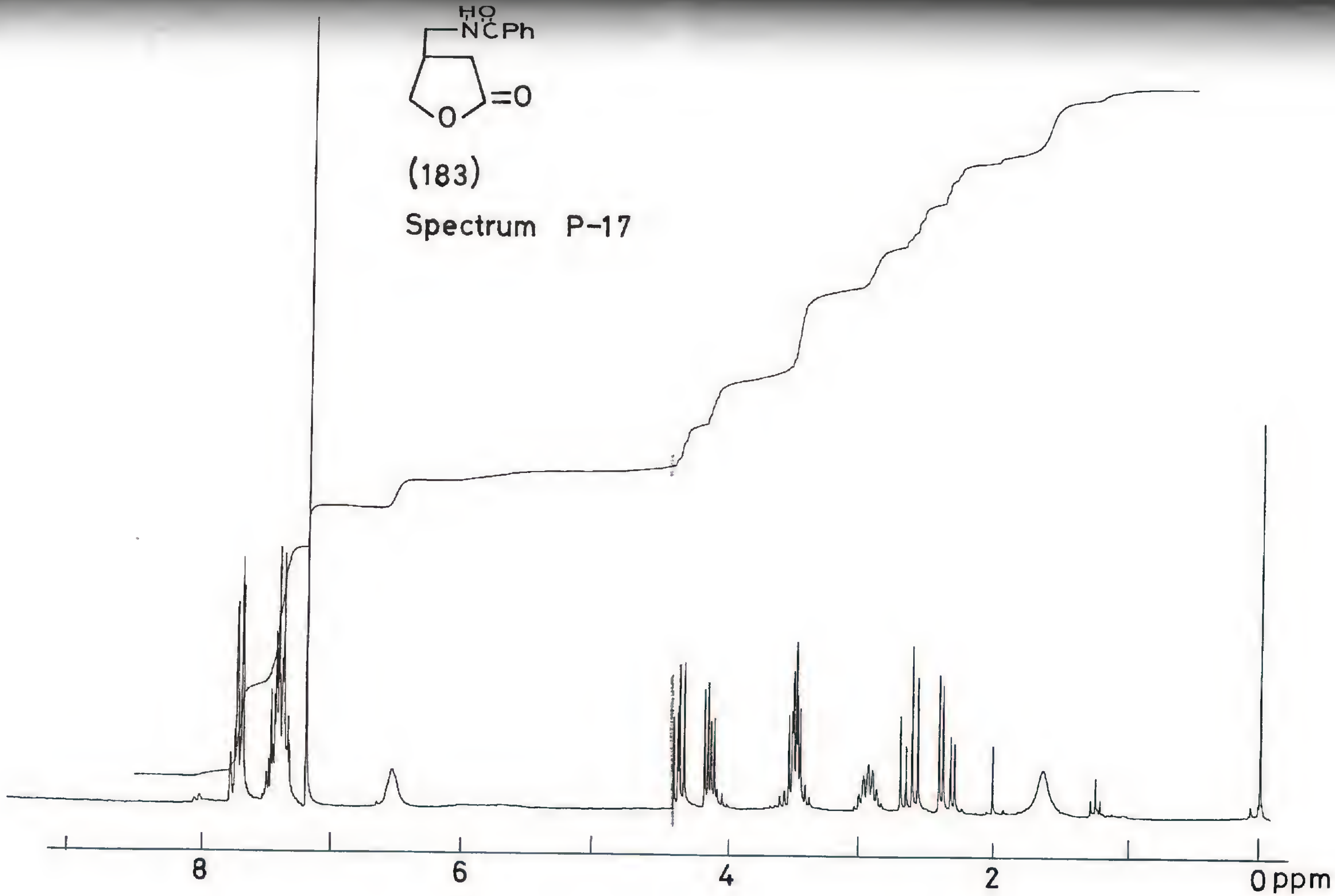
Spectrum P–16



(120a)

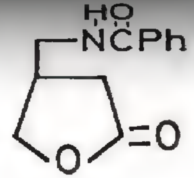
Spectrum C-16





(183)

Spectrum P-17



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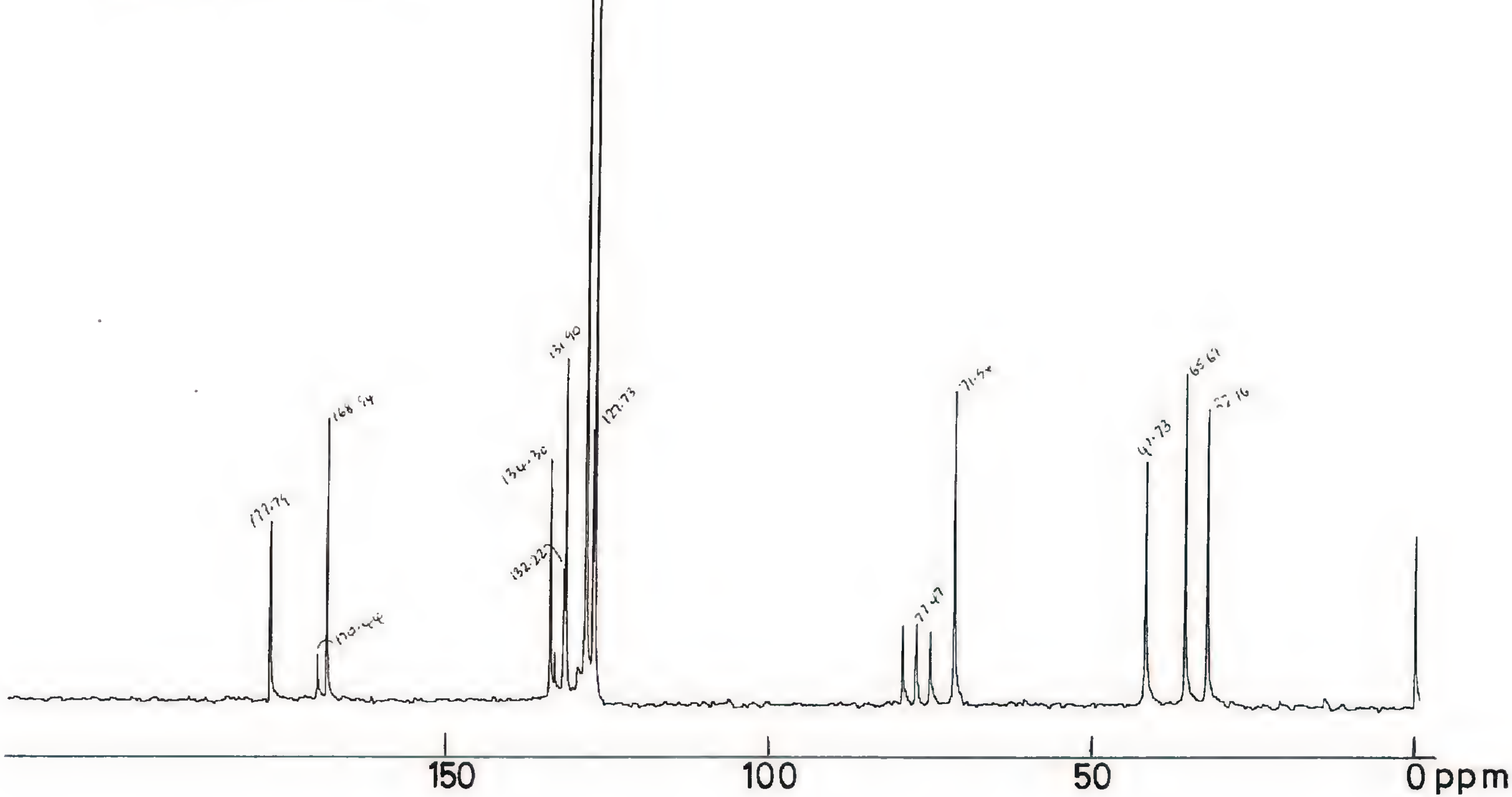
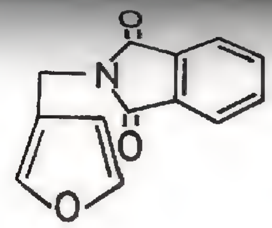
Spectrum C-17





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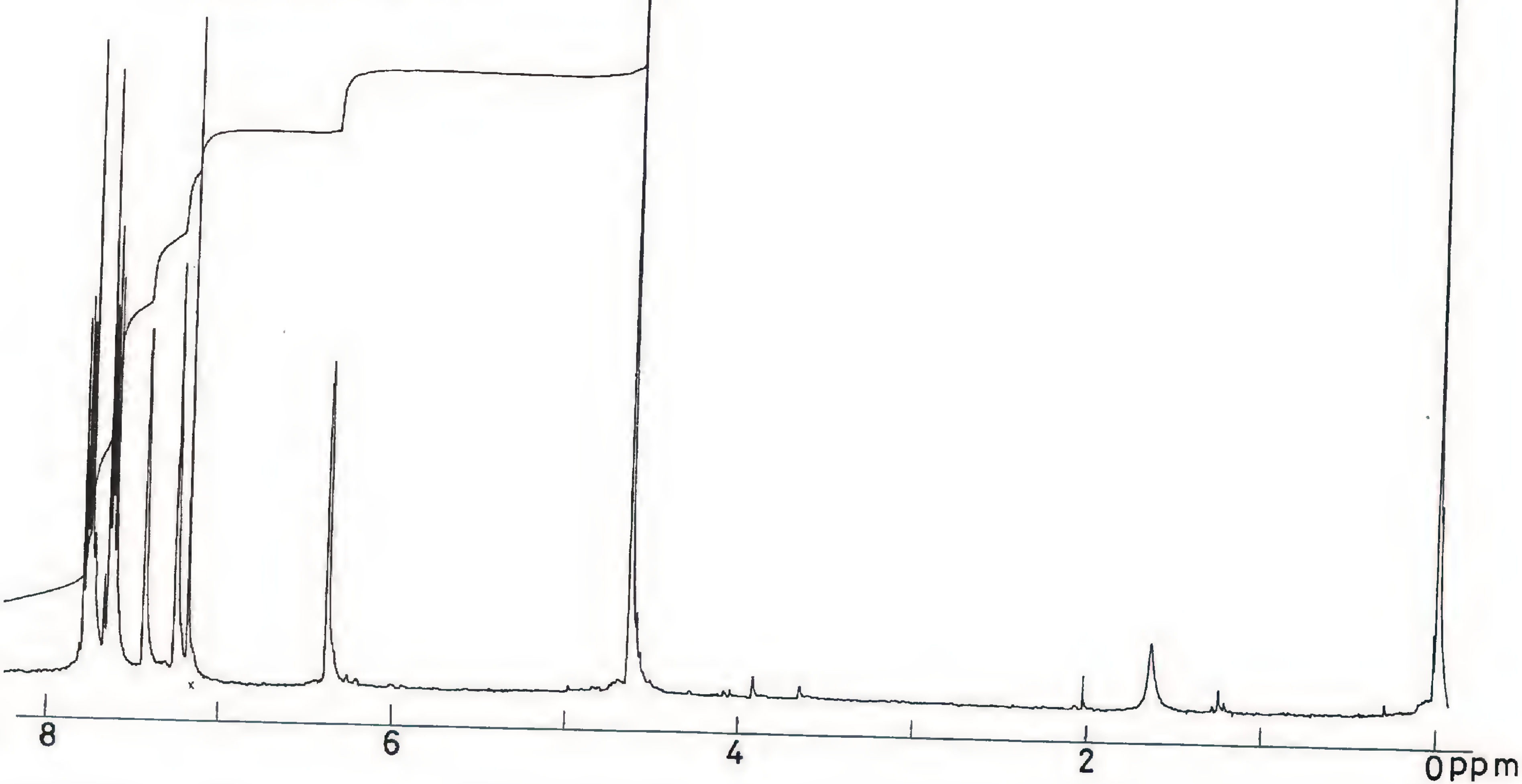
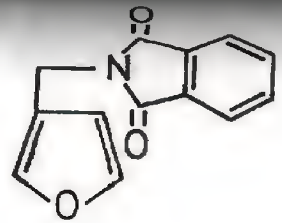
Spectrum P-18





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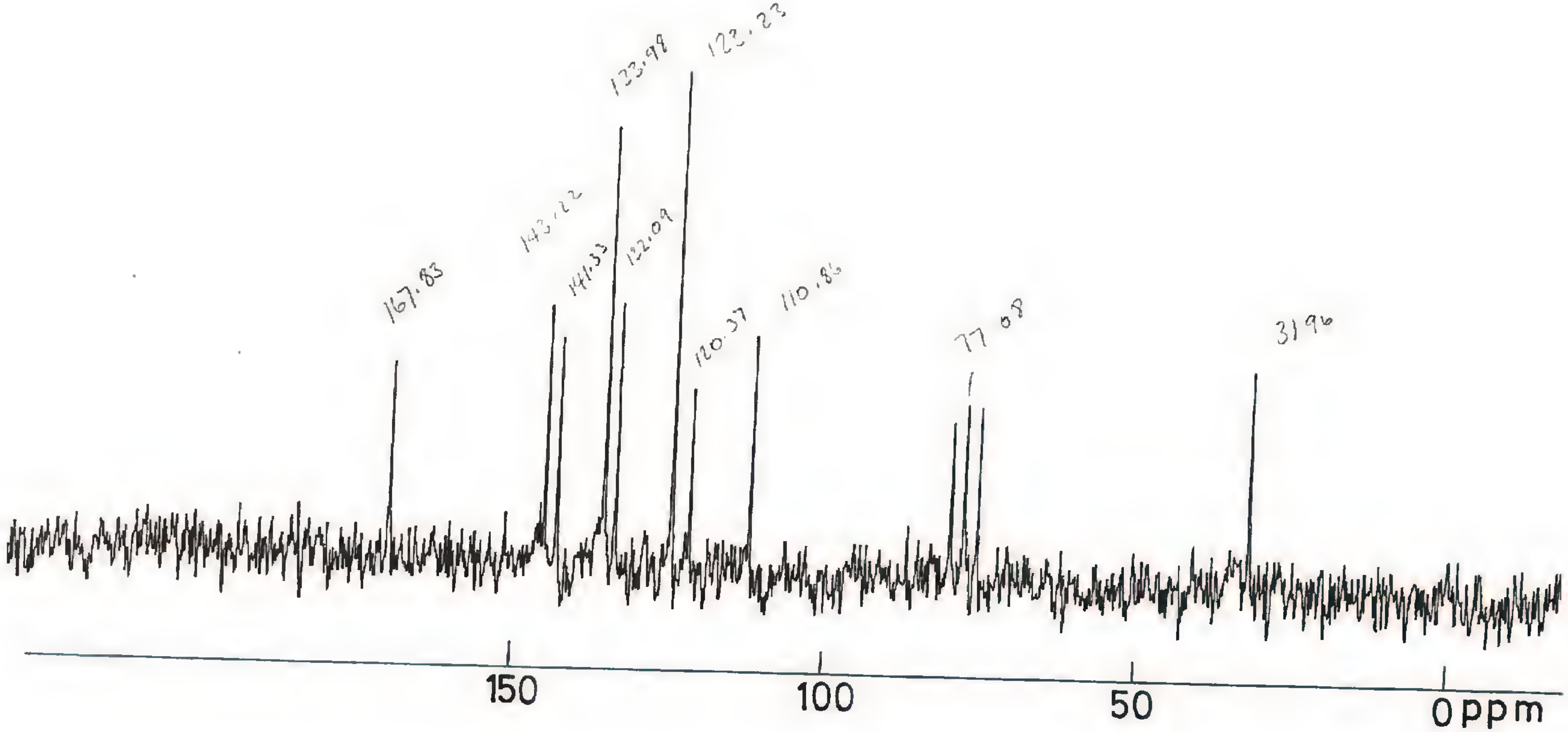
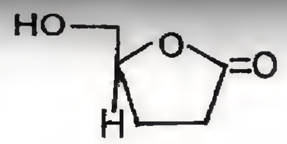
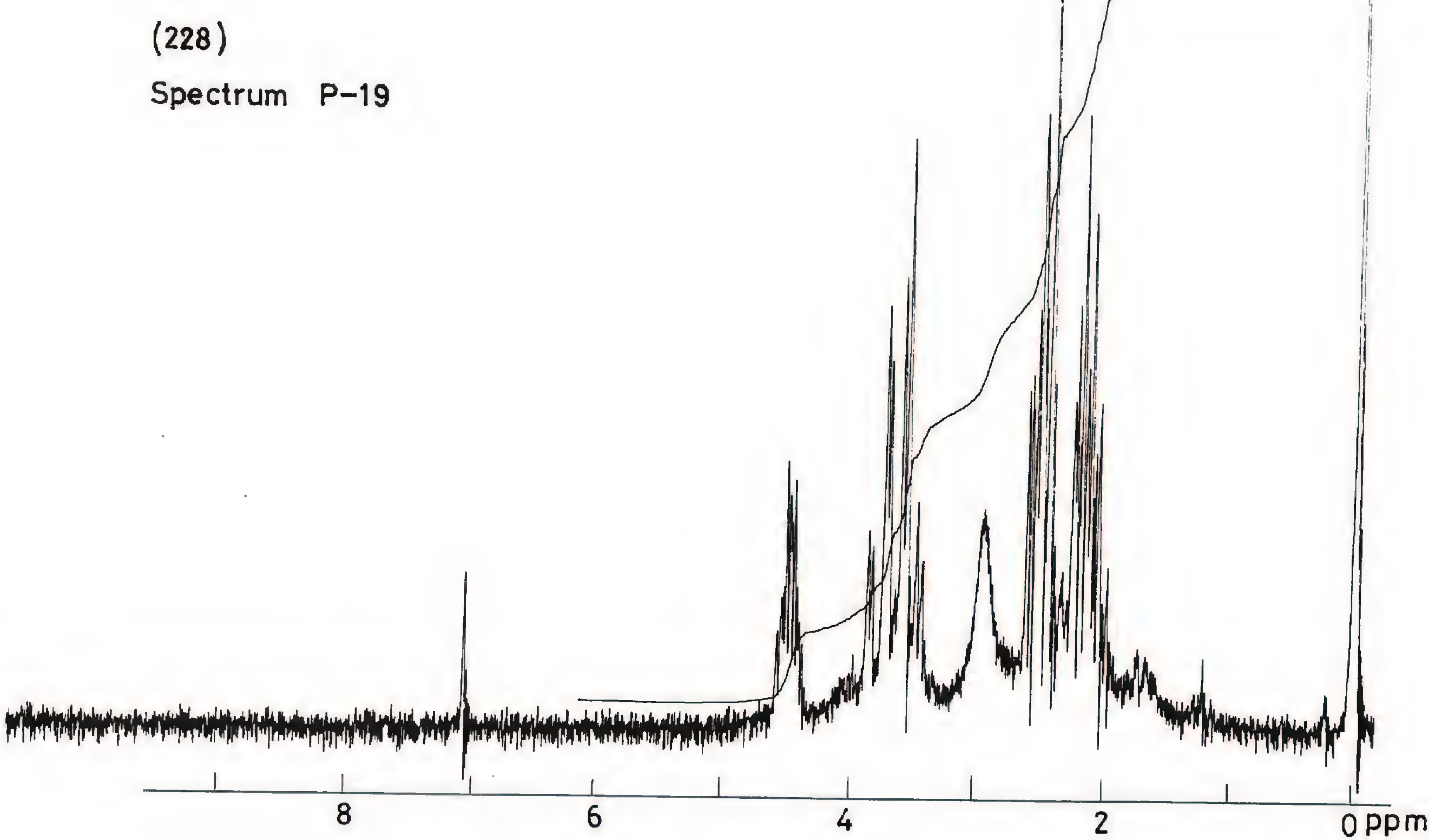
Spectrum C-18

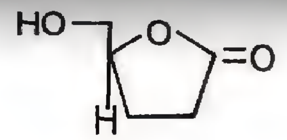




(228)

Spectrum P-19





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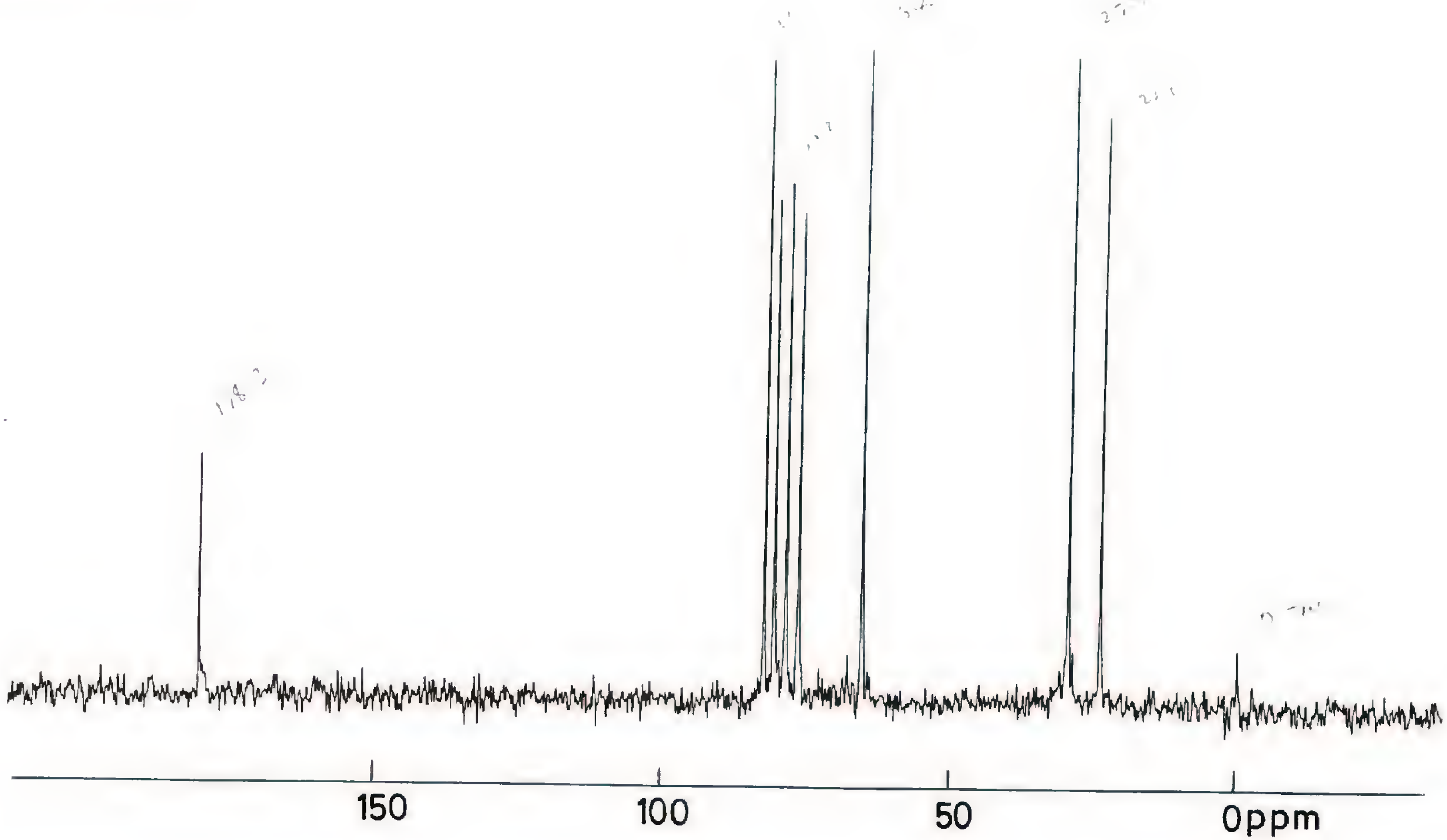
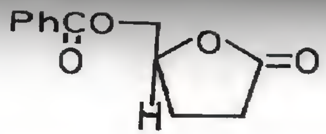
Spectrum C-19





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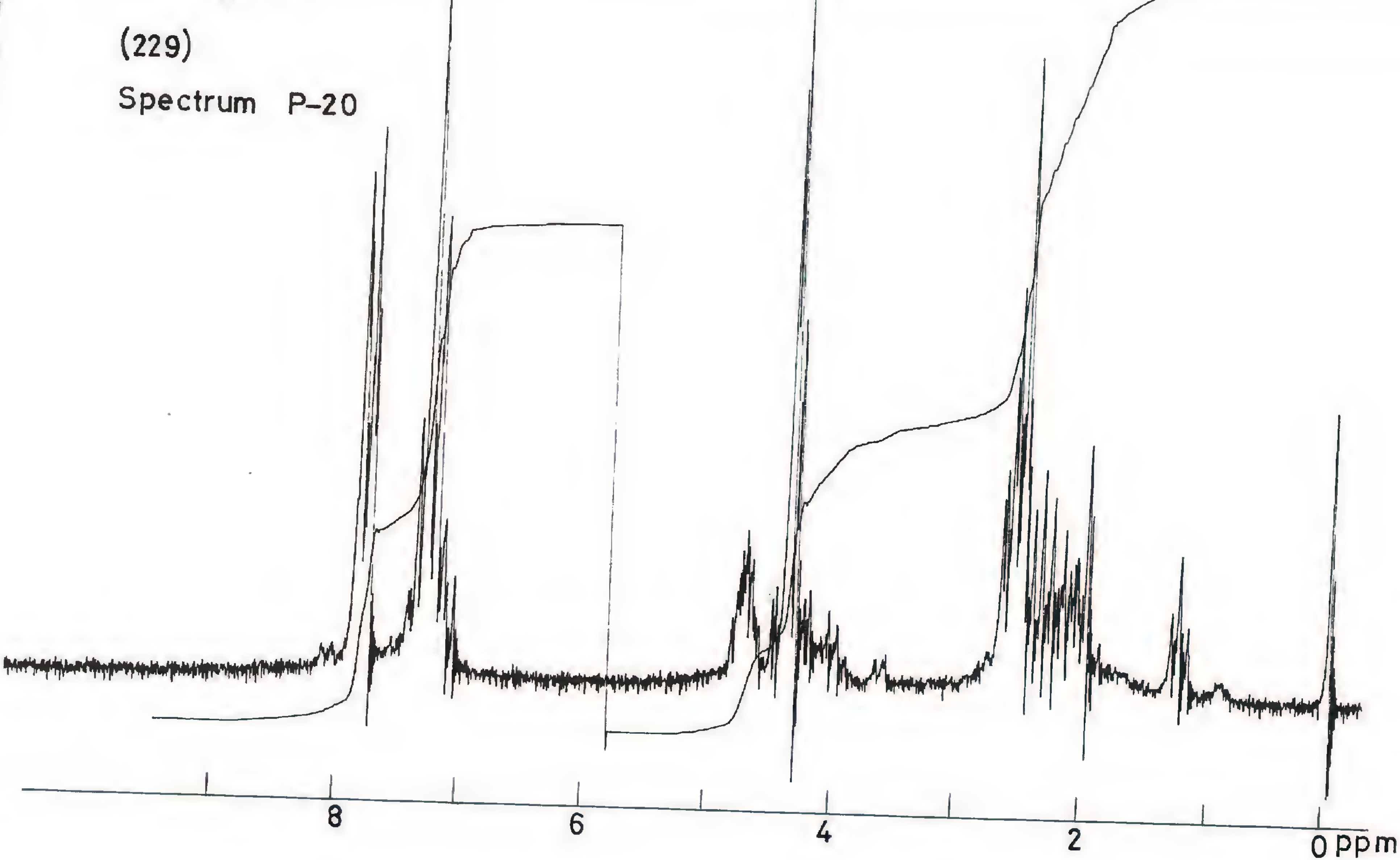
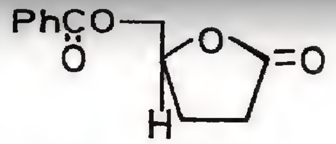
Spectrum P-20





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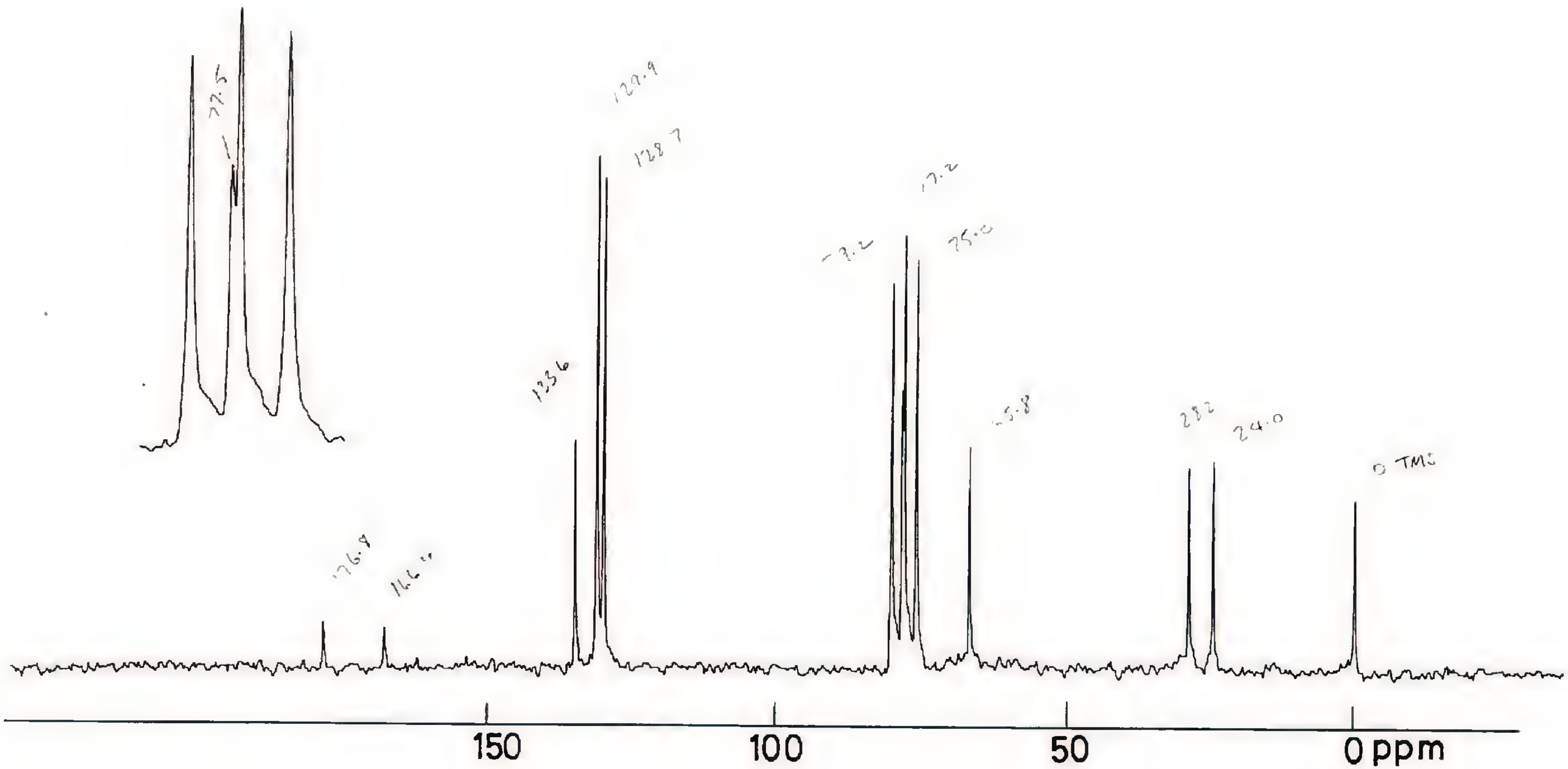
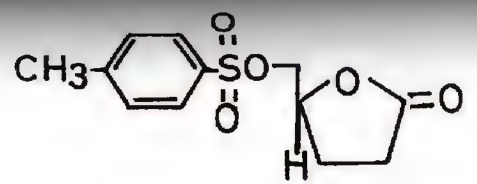
Spectrum C-20





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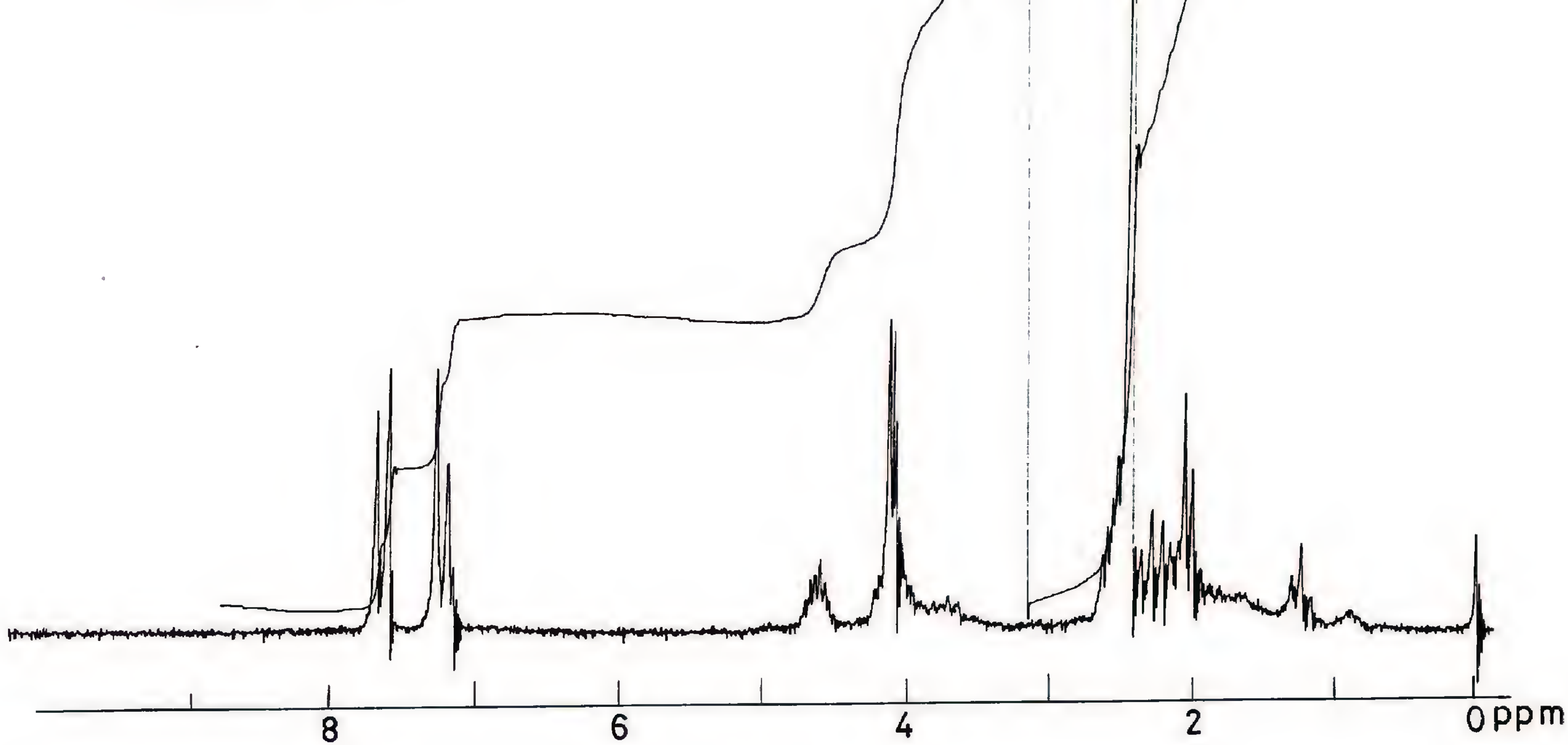
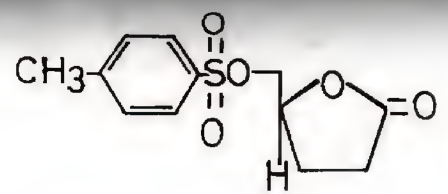
Spectrum P-21





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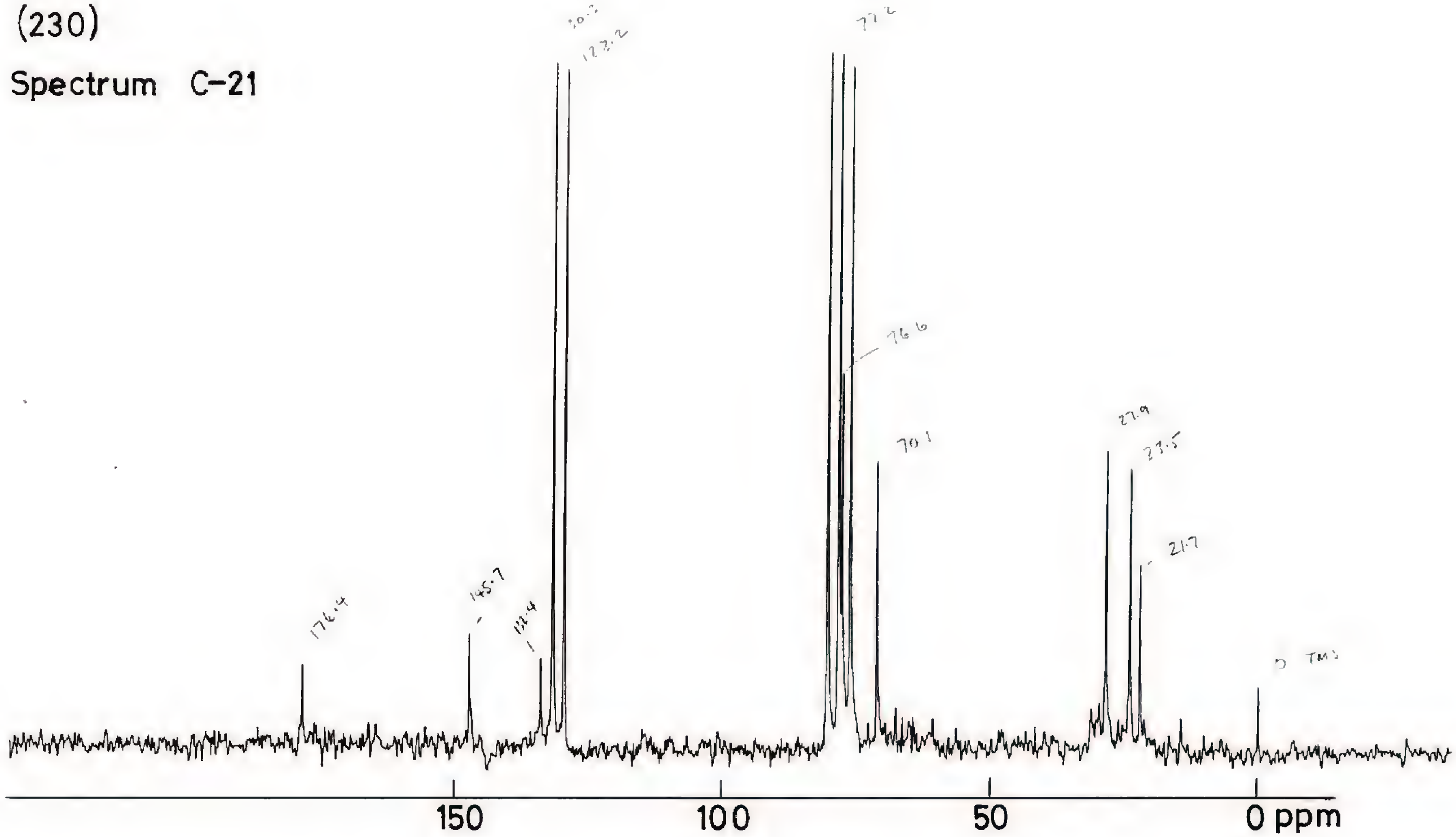
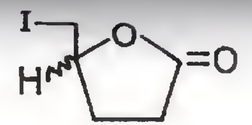
Spectrum C–21





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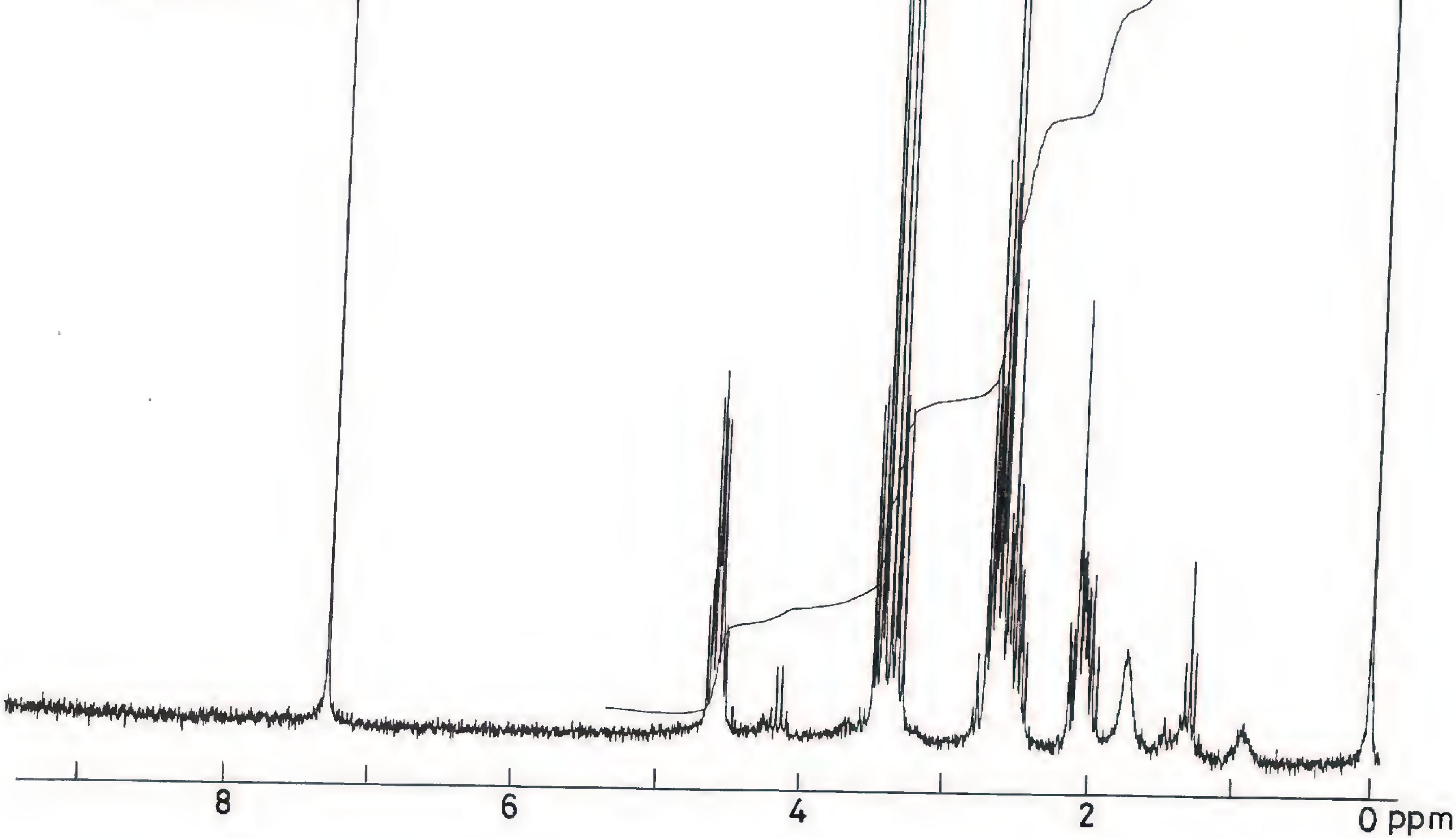
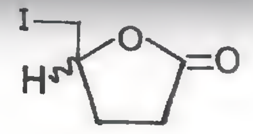
Spectrum P-22





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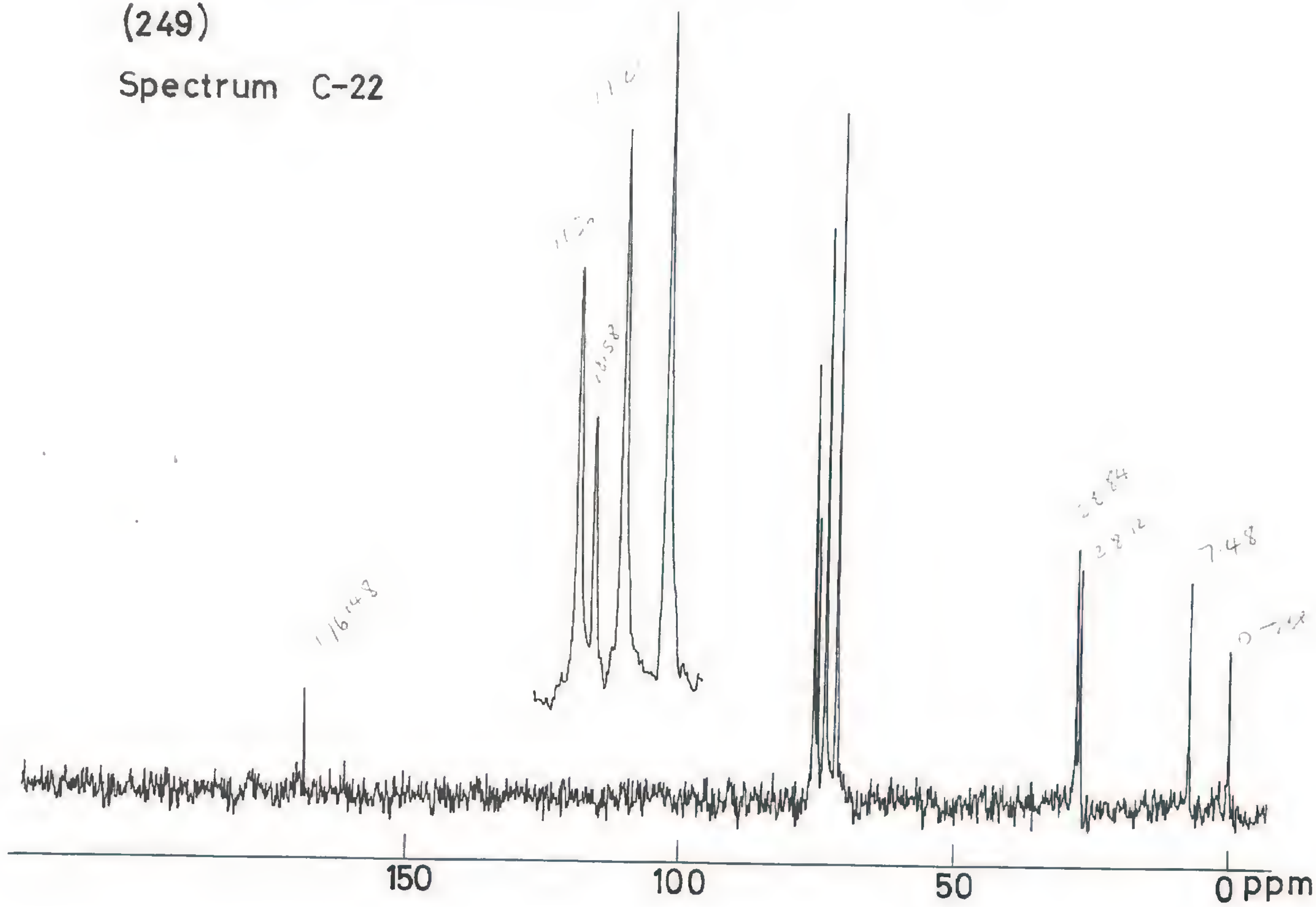
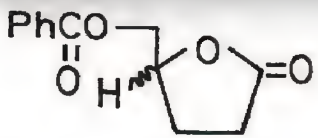
Spectrum C-22





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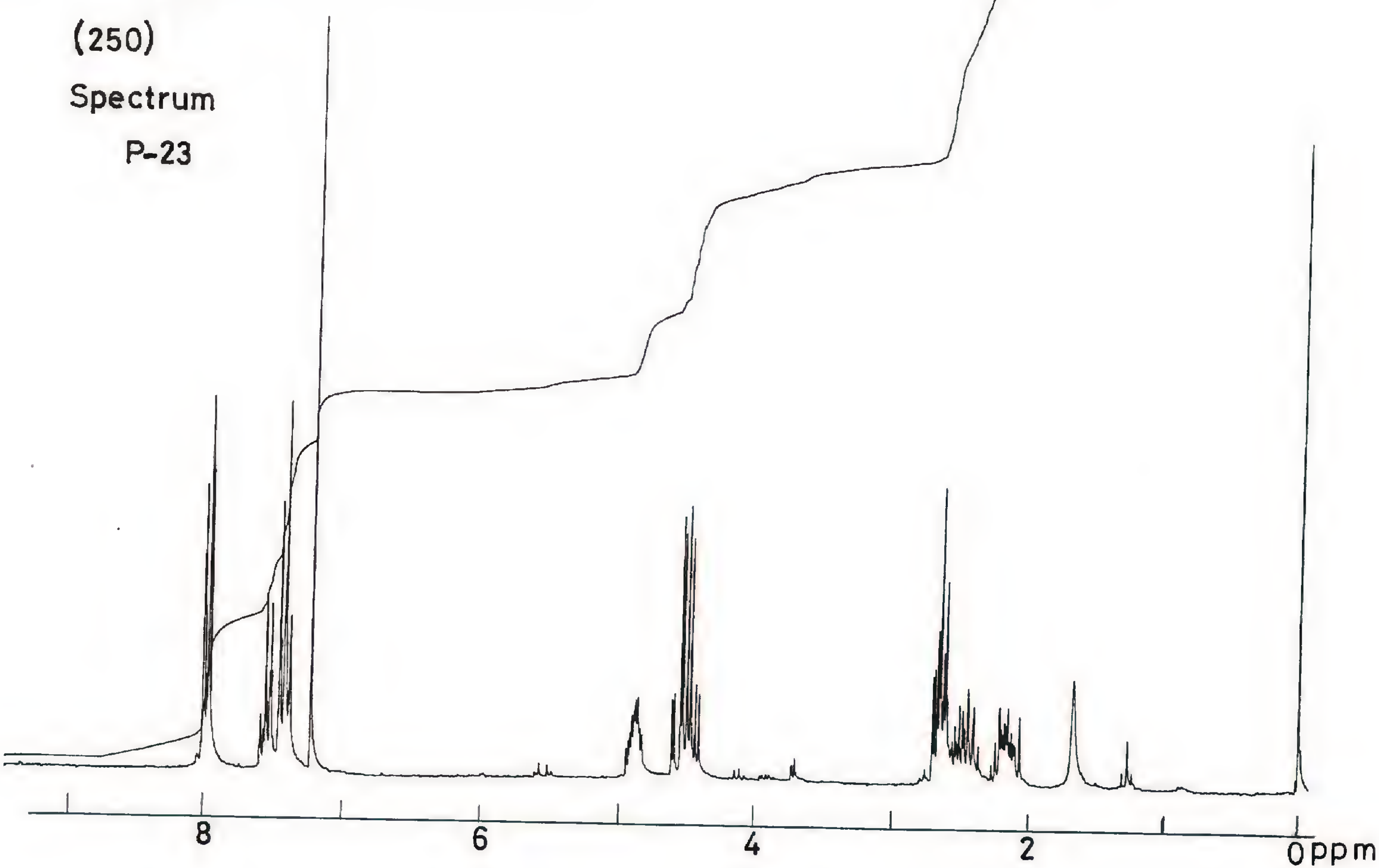
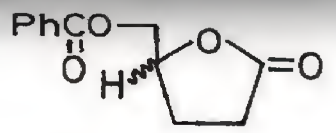
Spectrum

P-23





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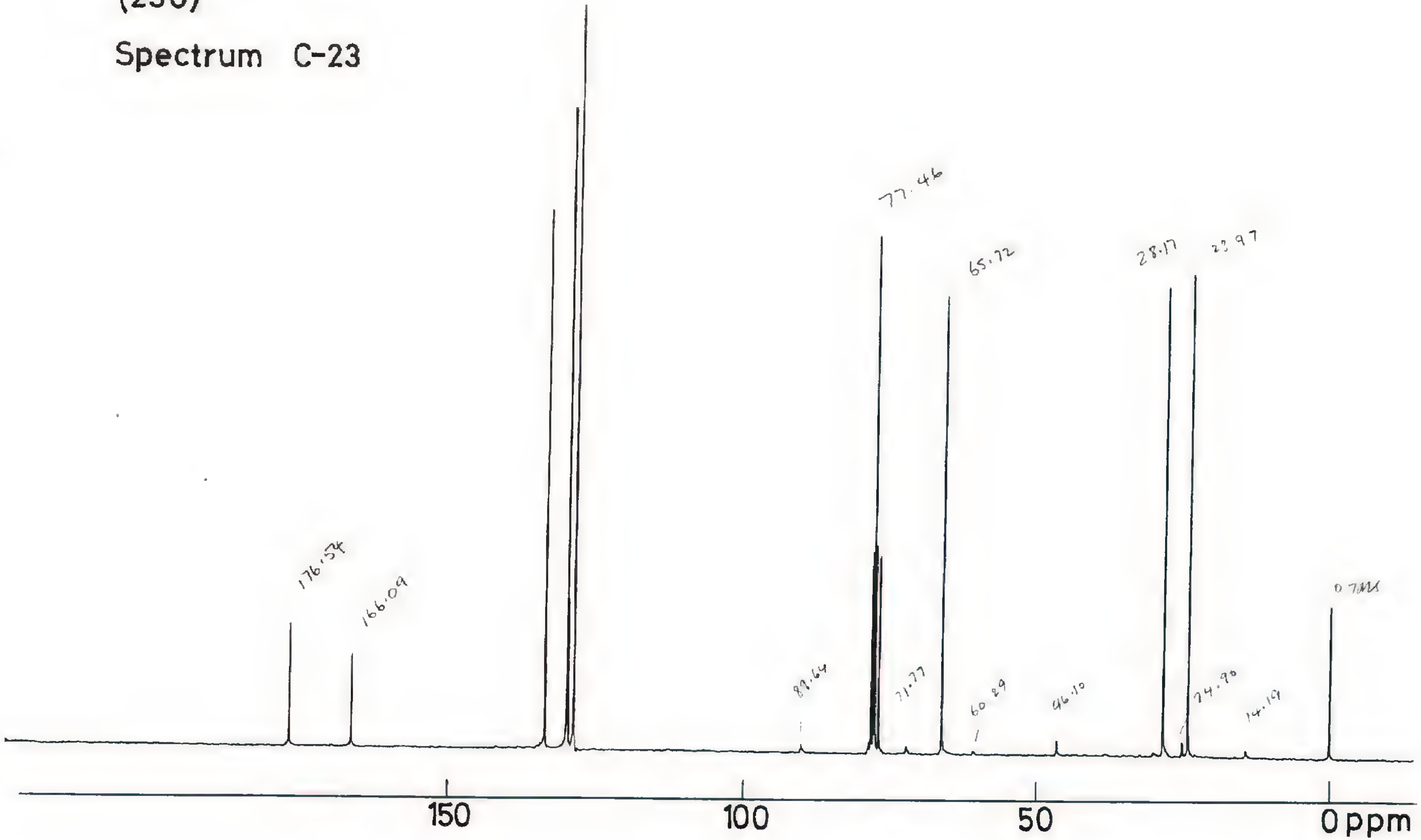

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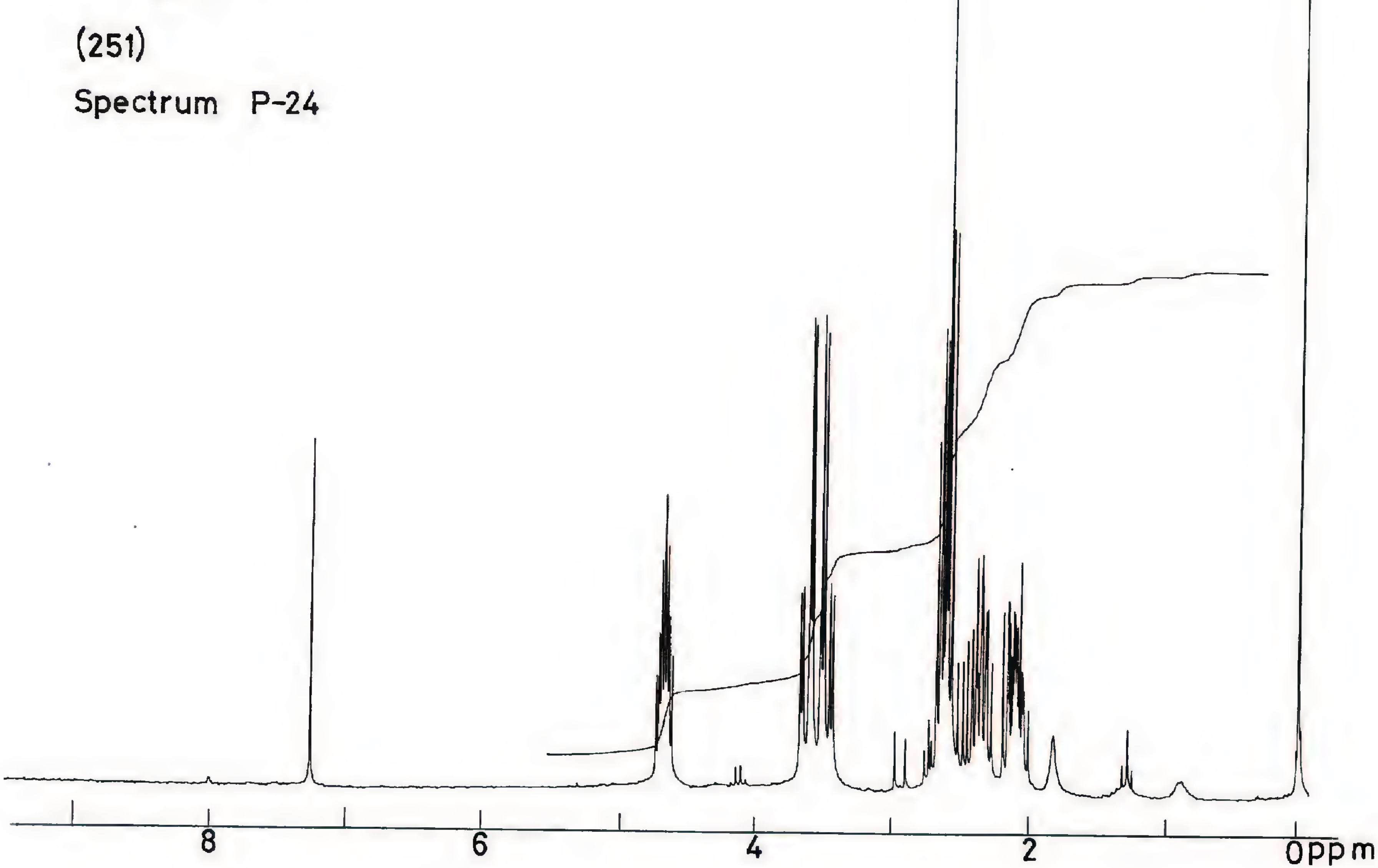
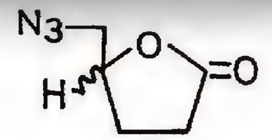
Spectrum P-24





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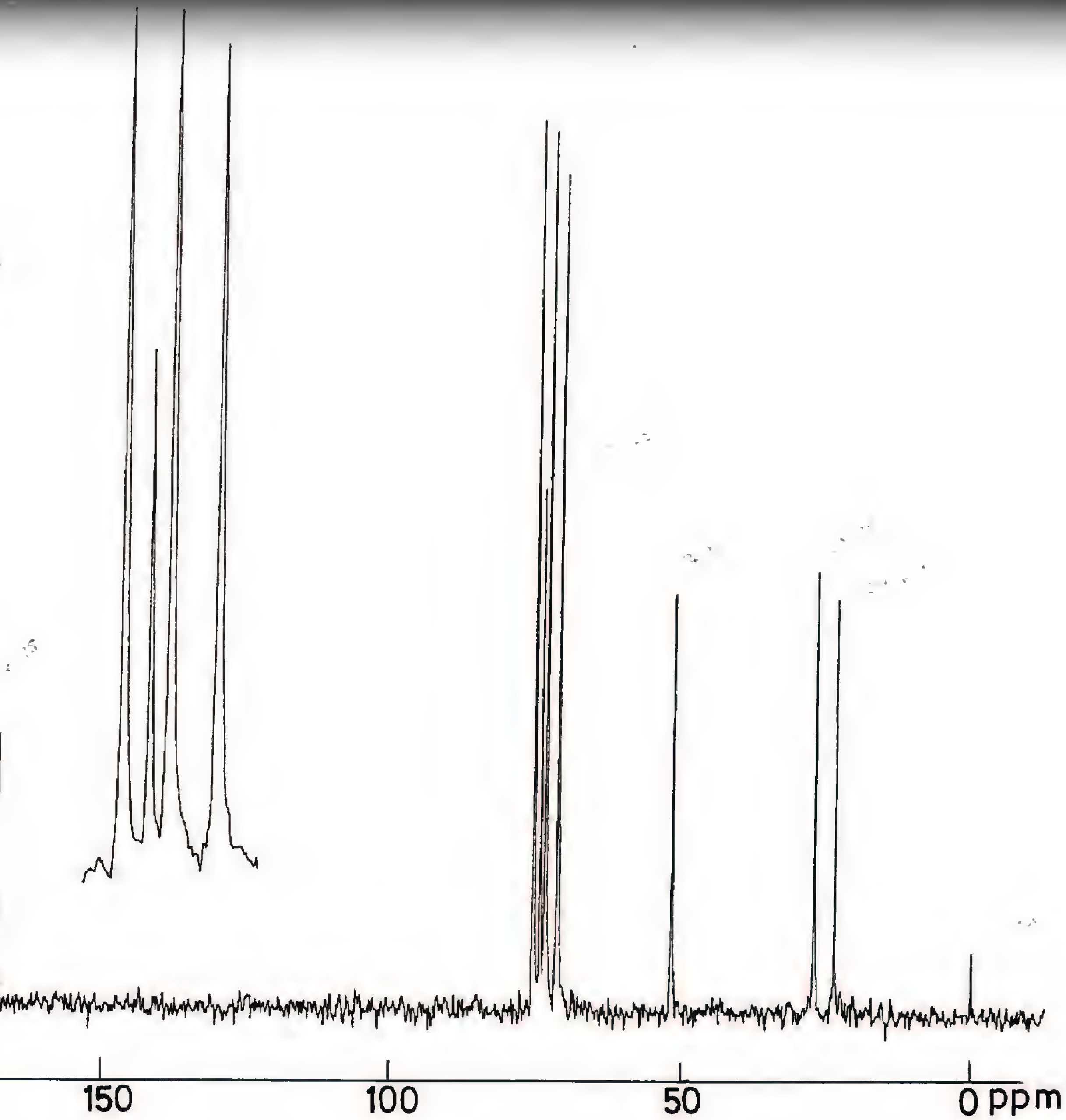

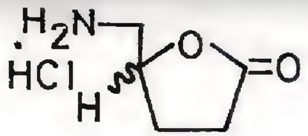

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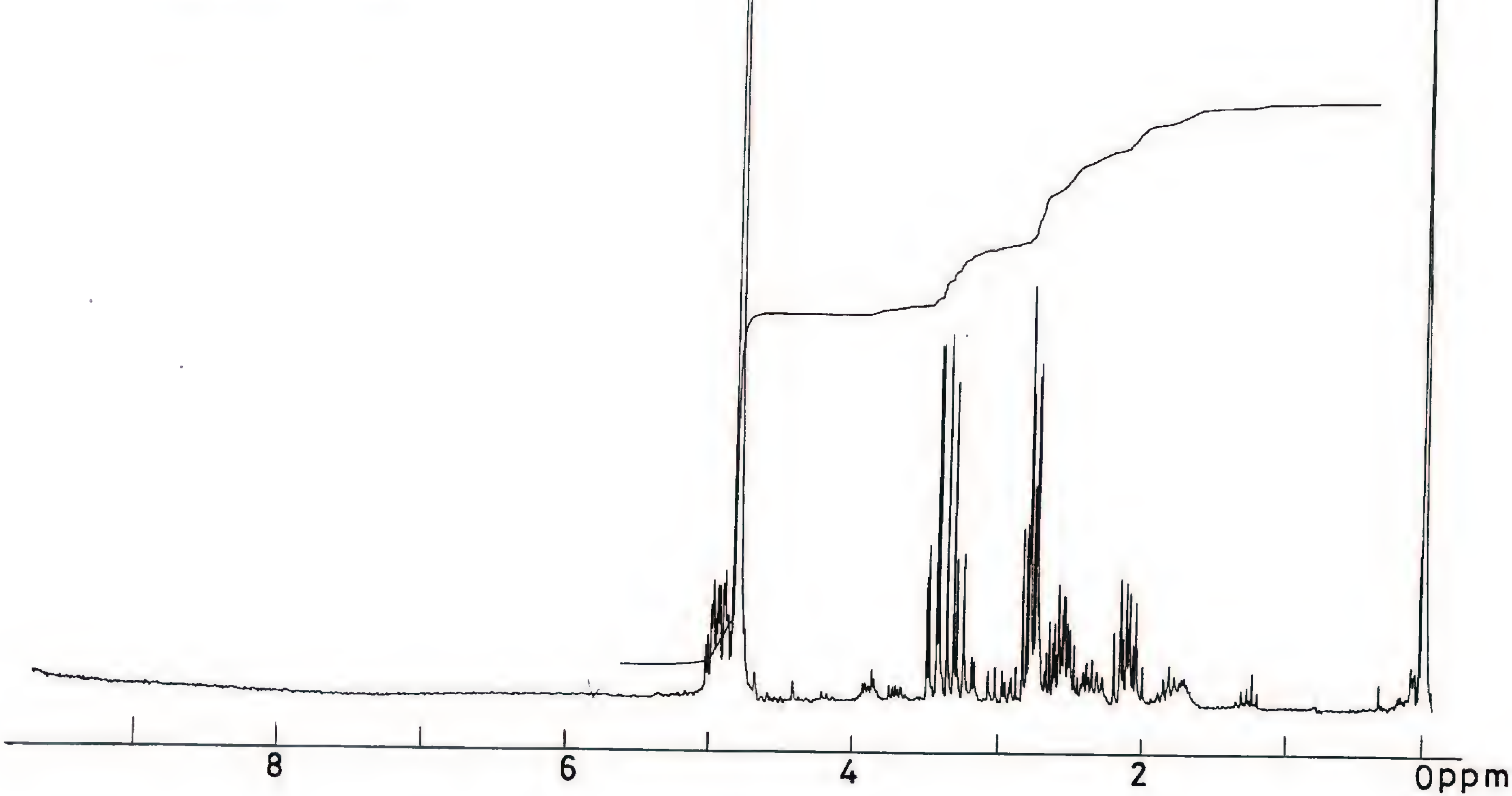

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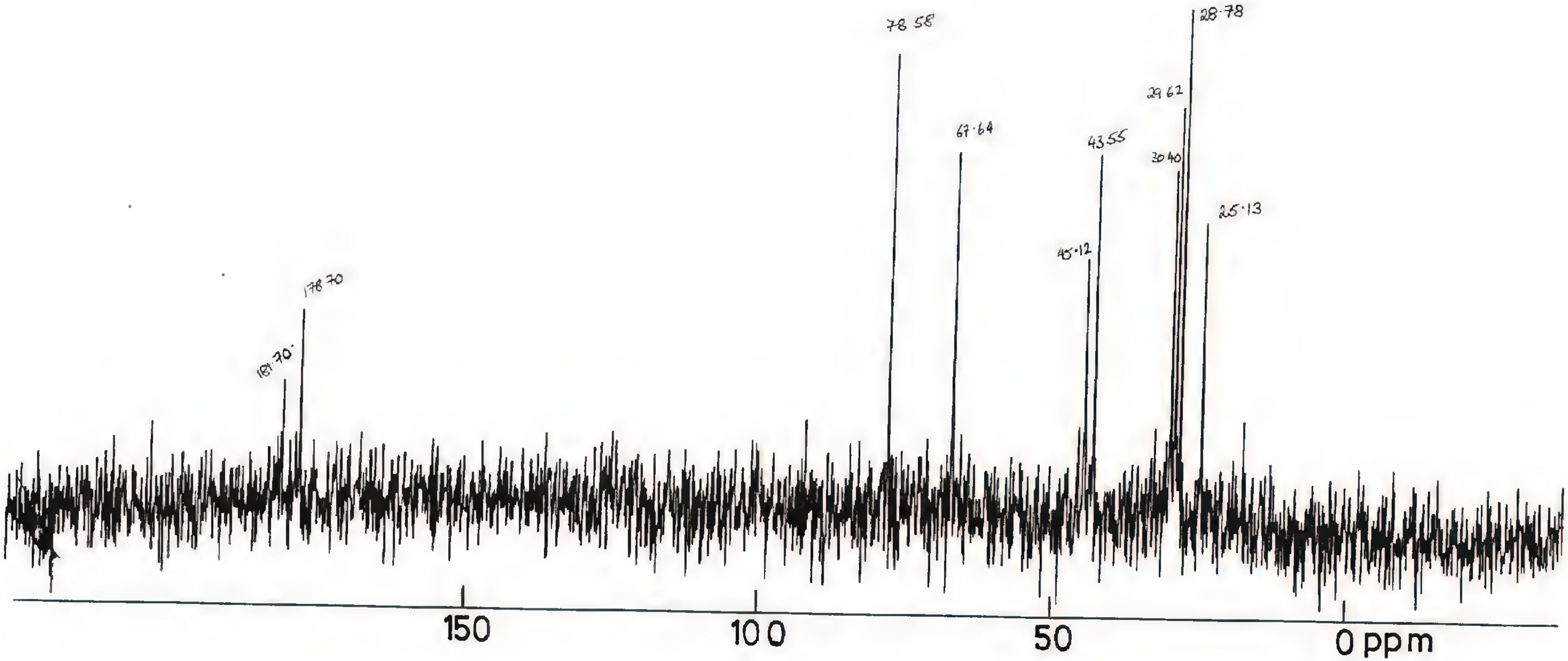

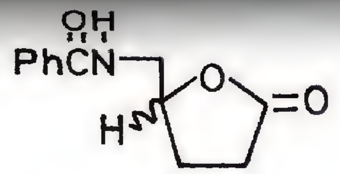

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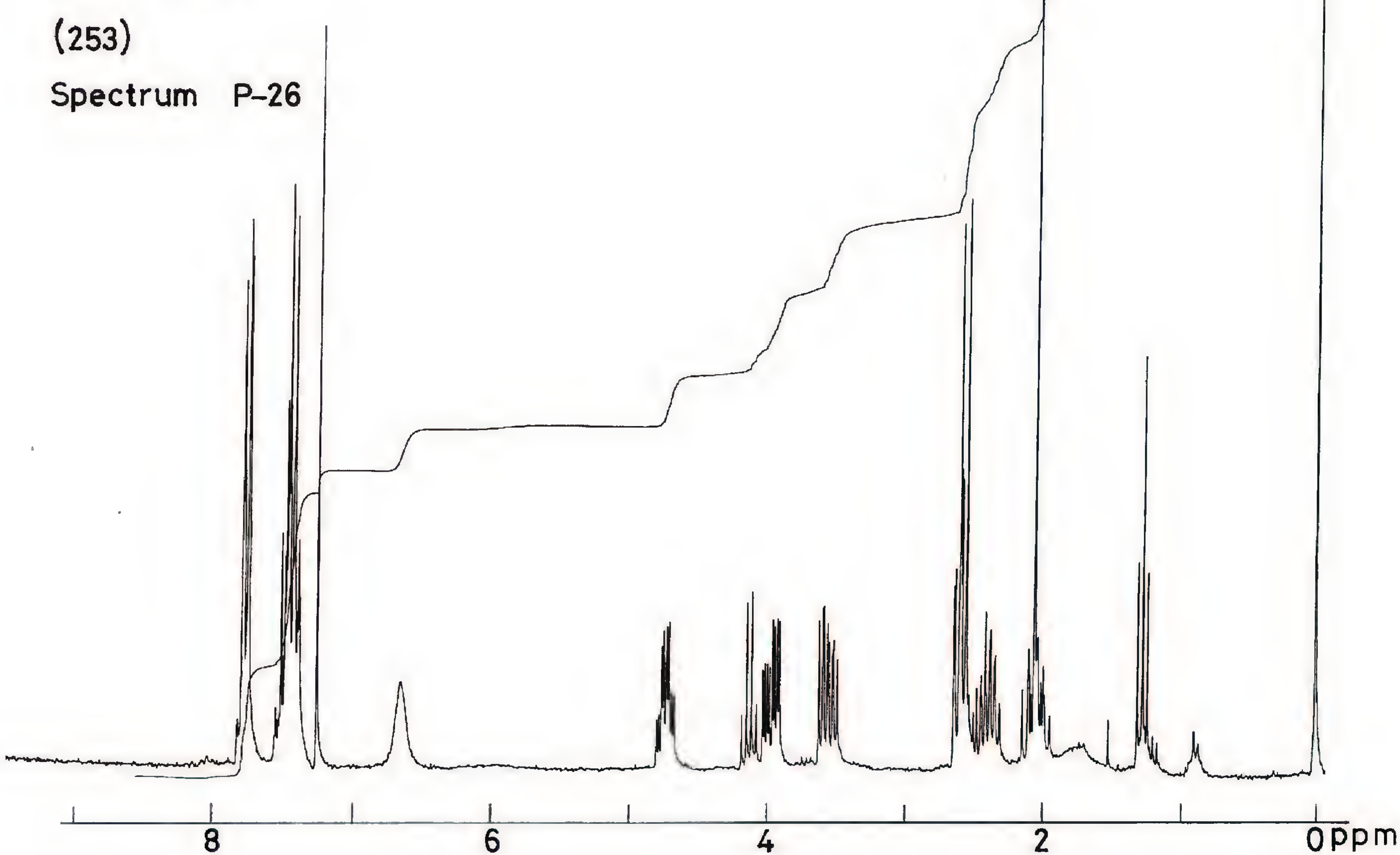
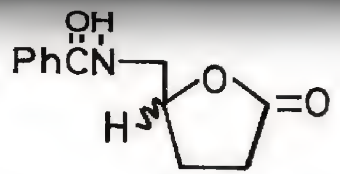
Spectrum P-26





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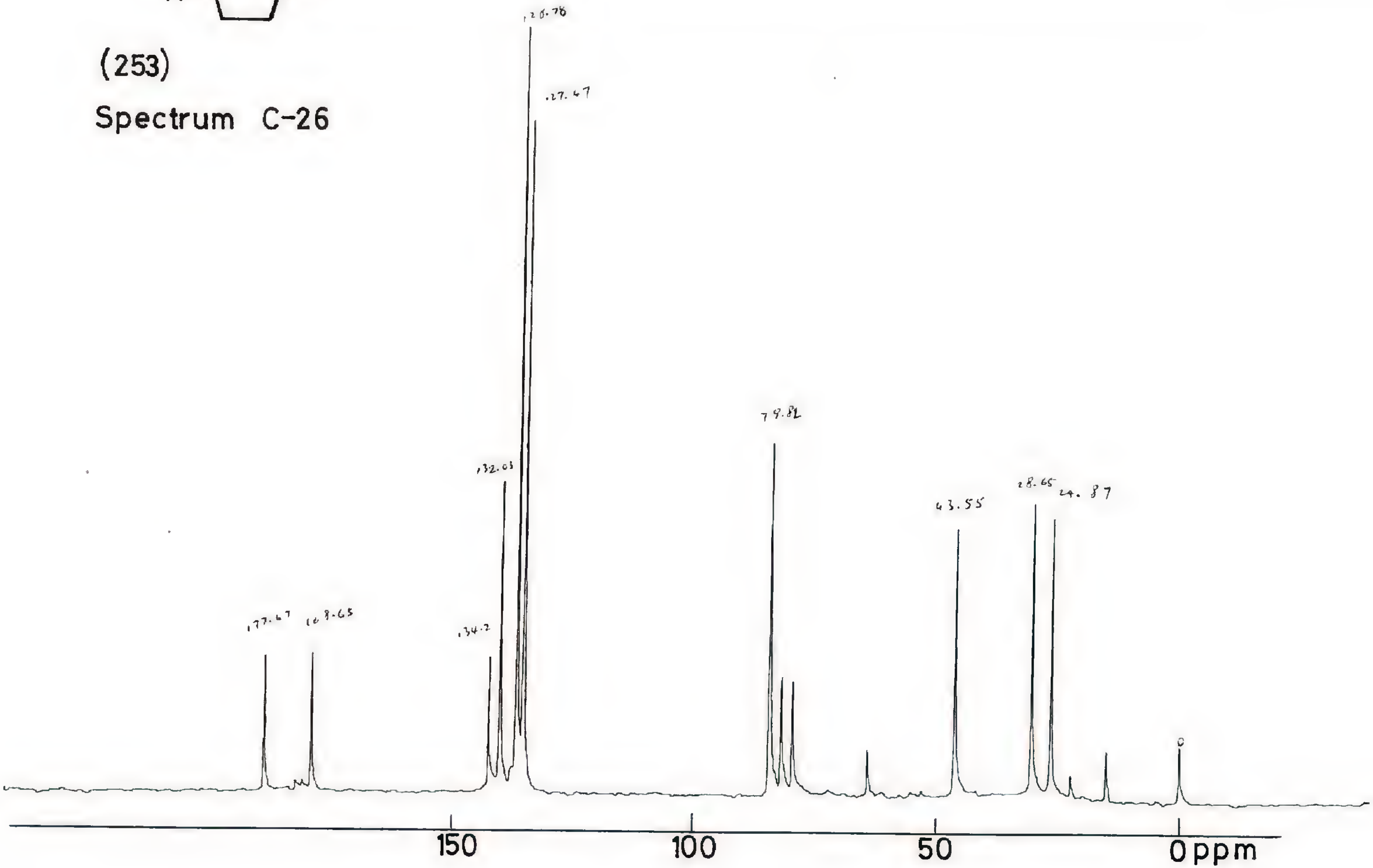

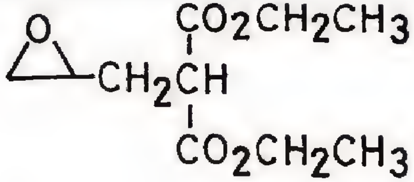

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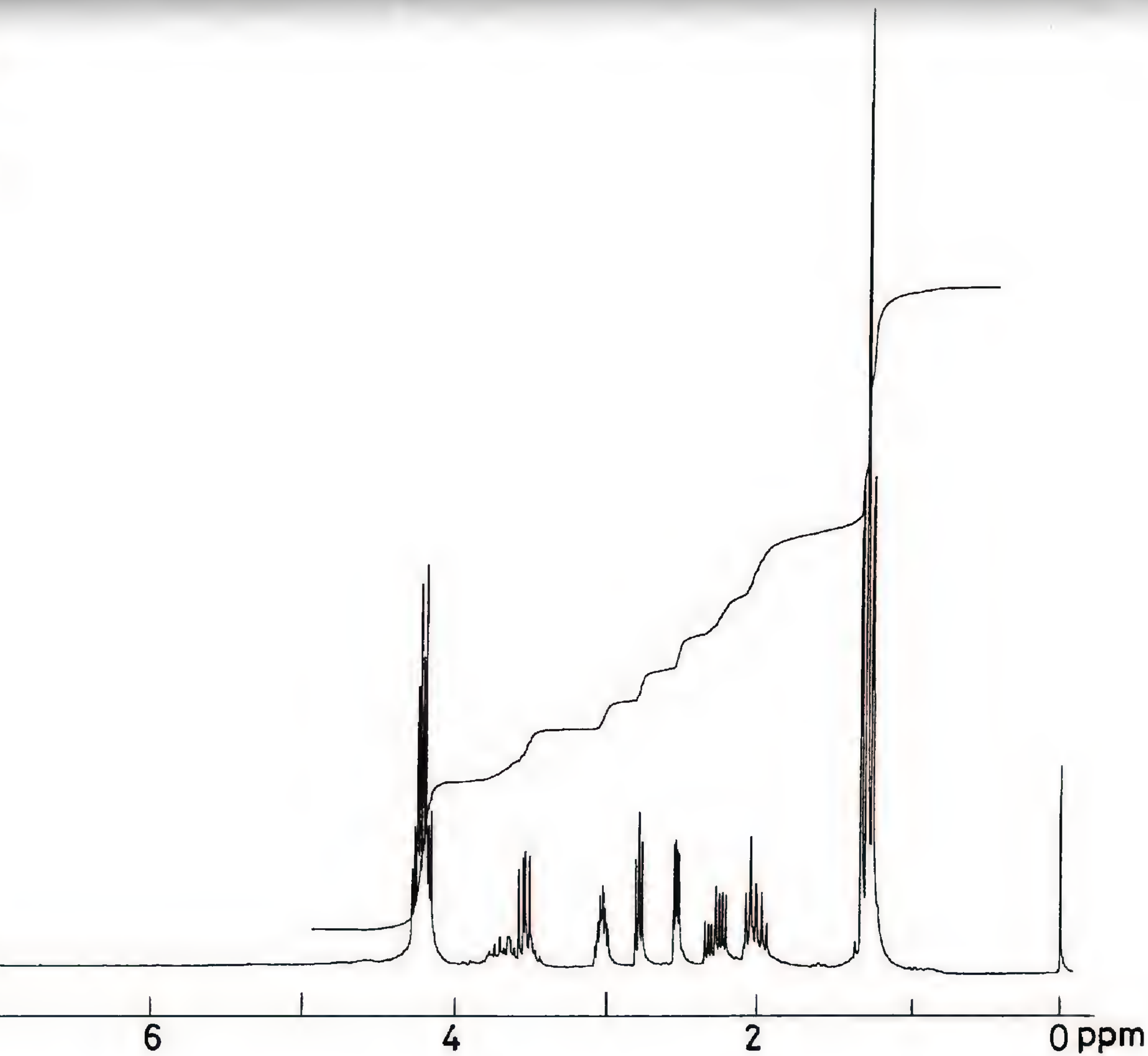

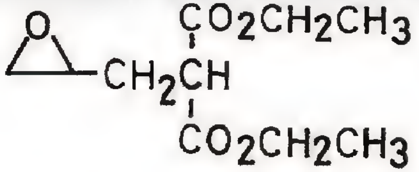

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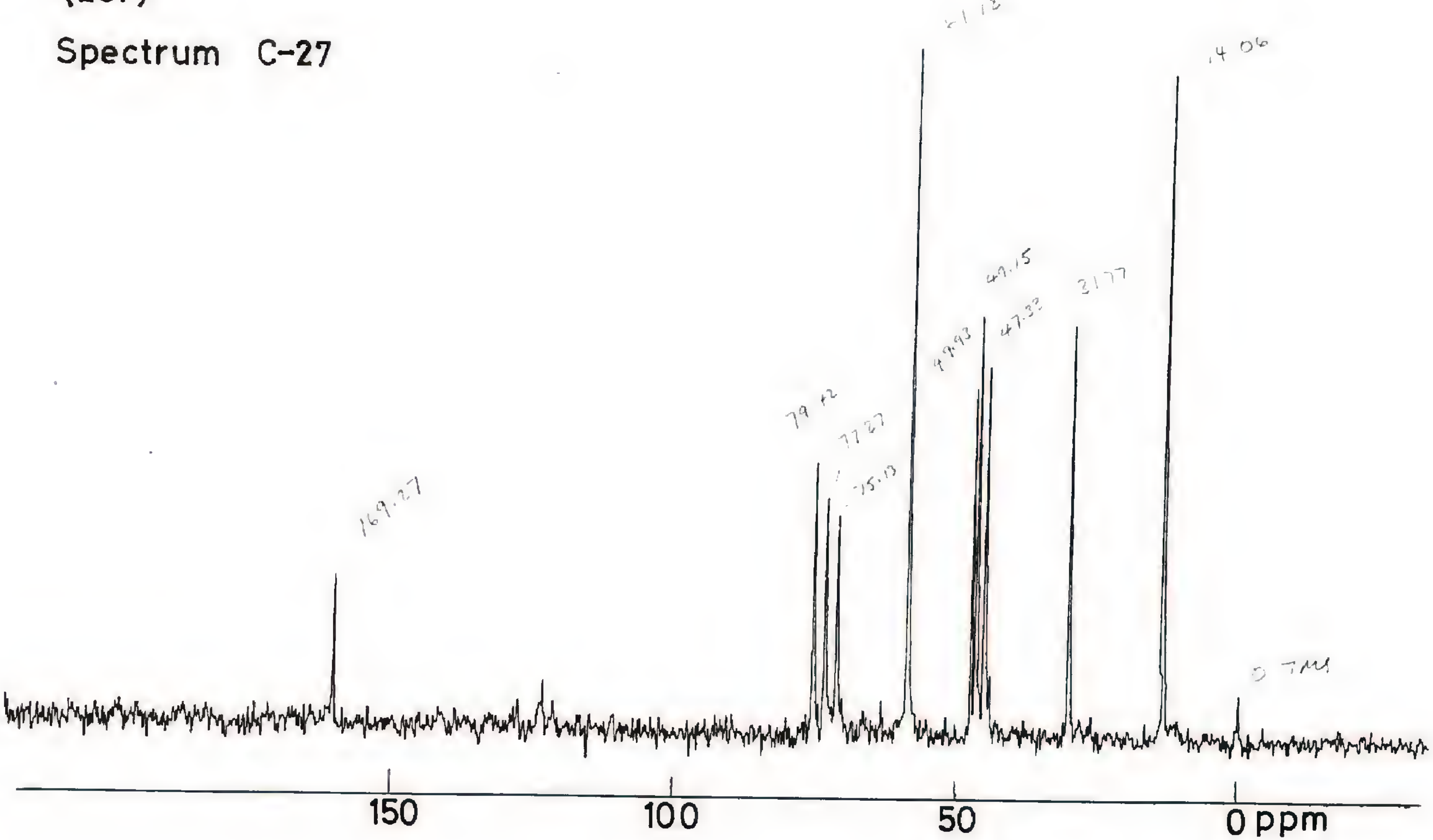
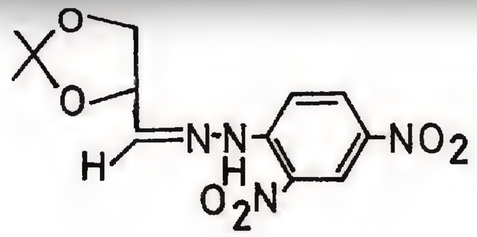
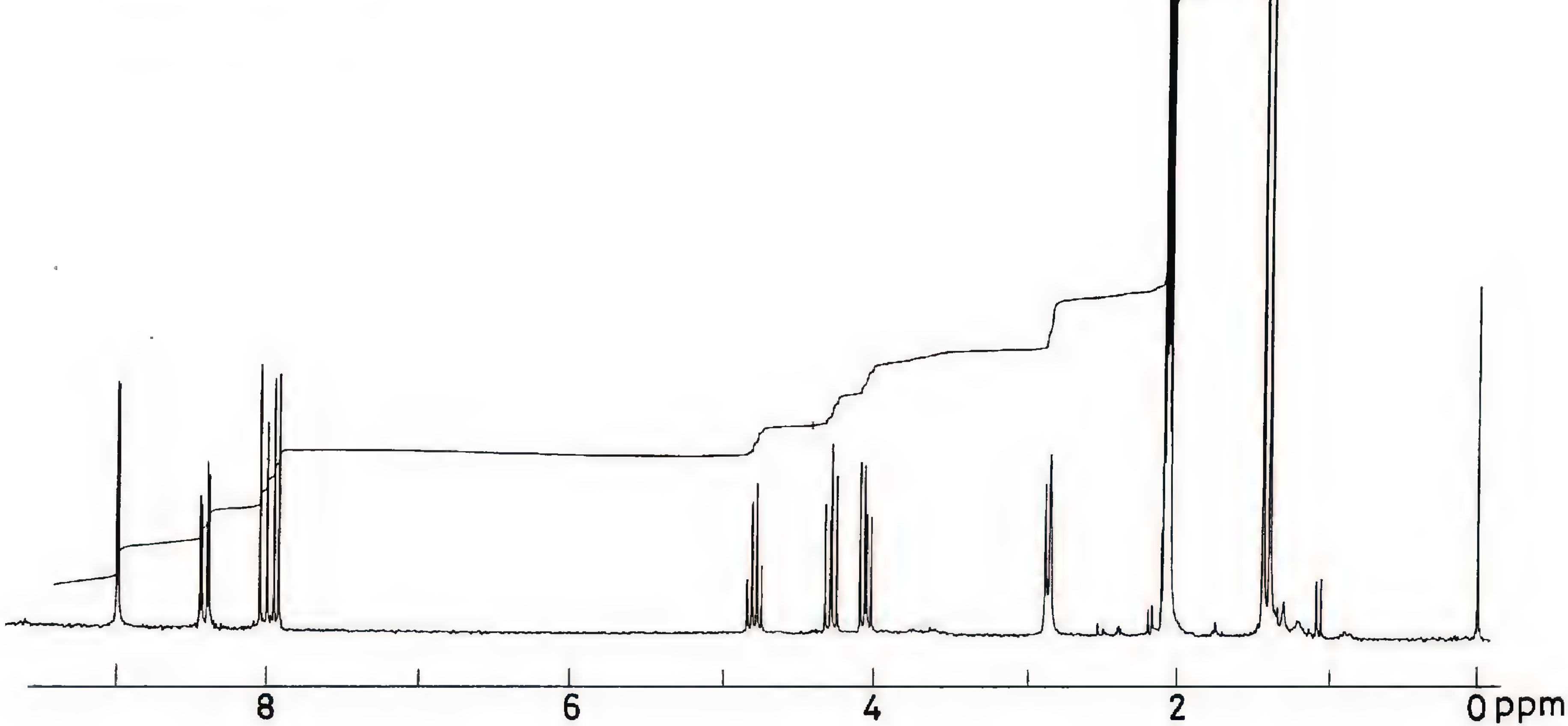
Spectrum C-27

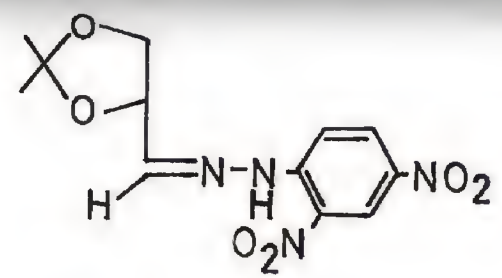




(268)

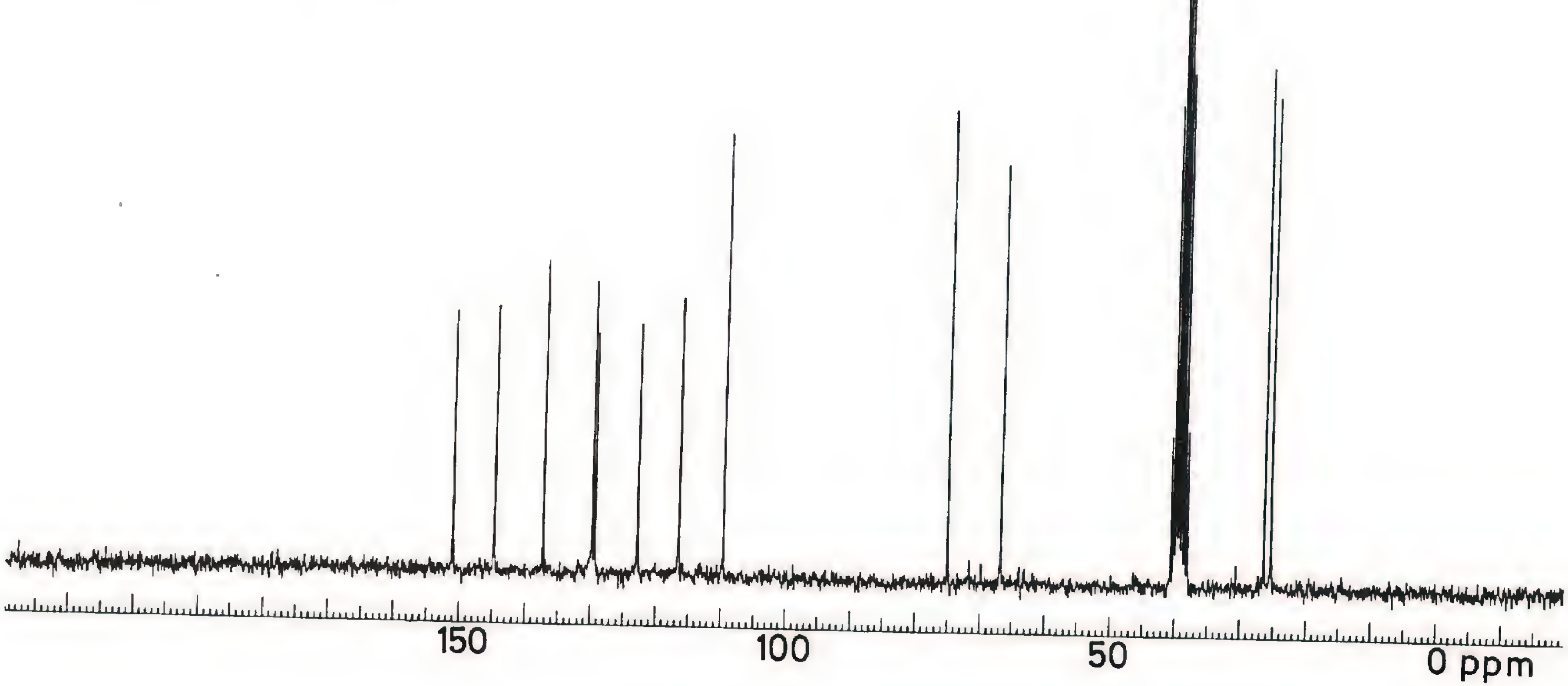
Spectrum P-28

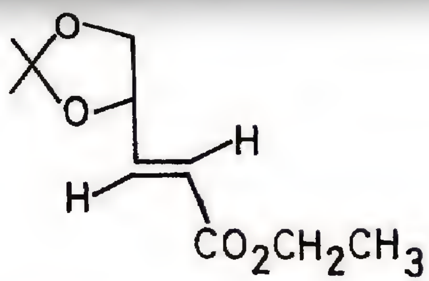




(268)

Spectrum C-28





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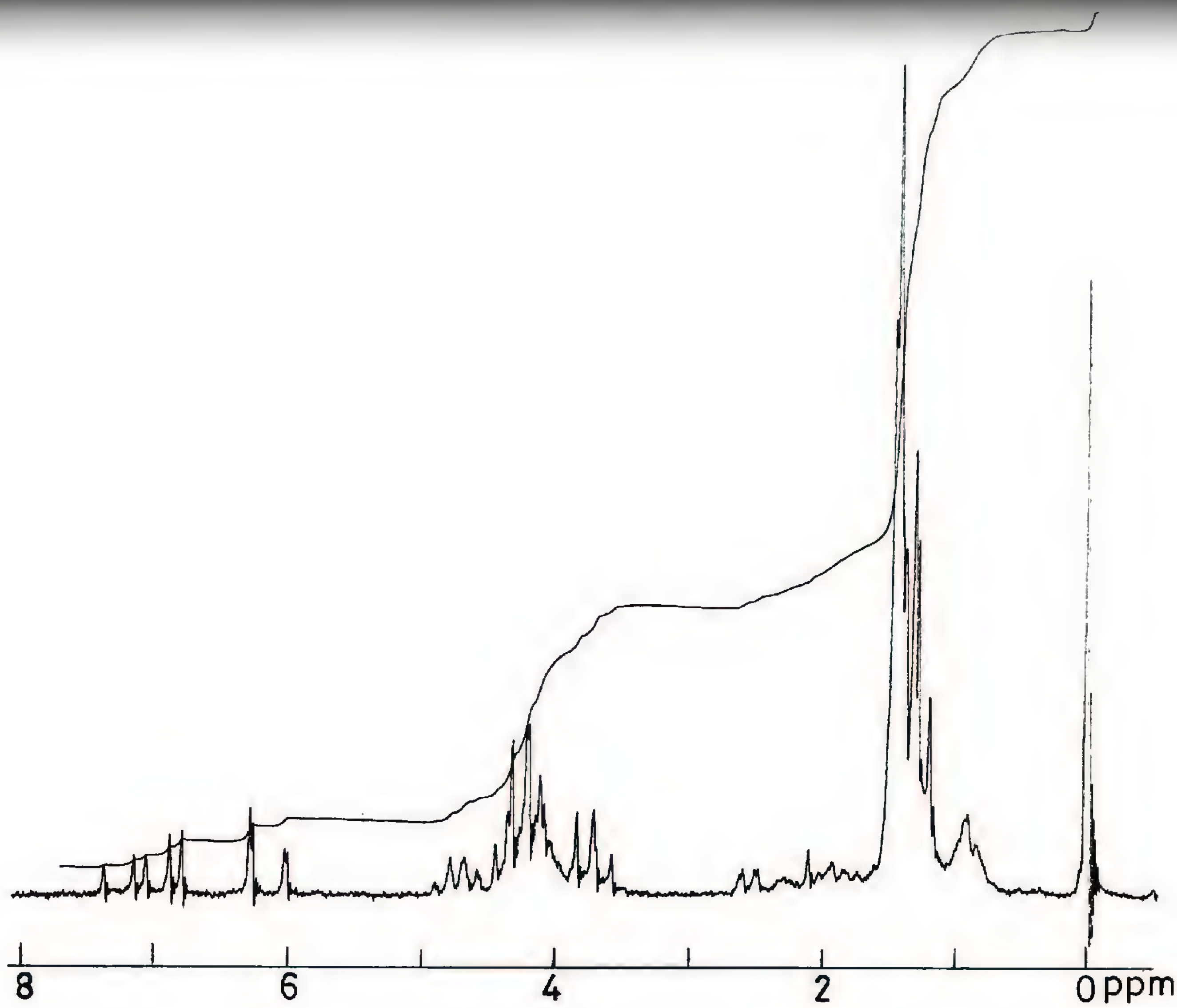
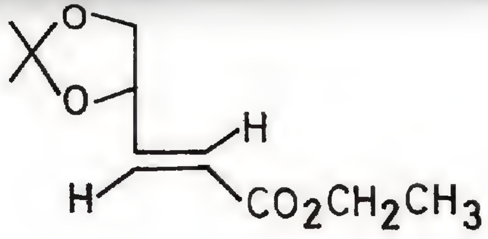
Spectrum P-29





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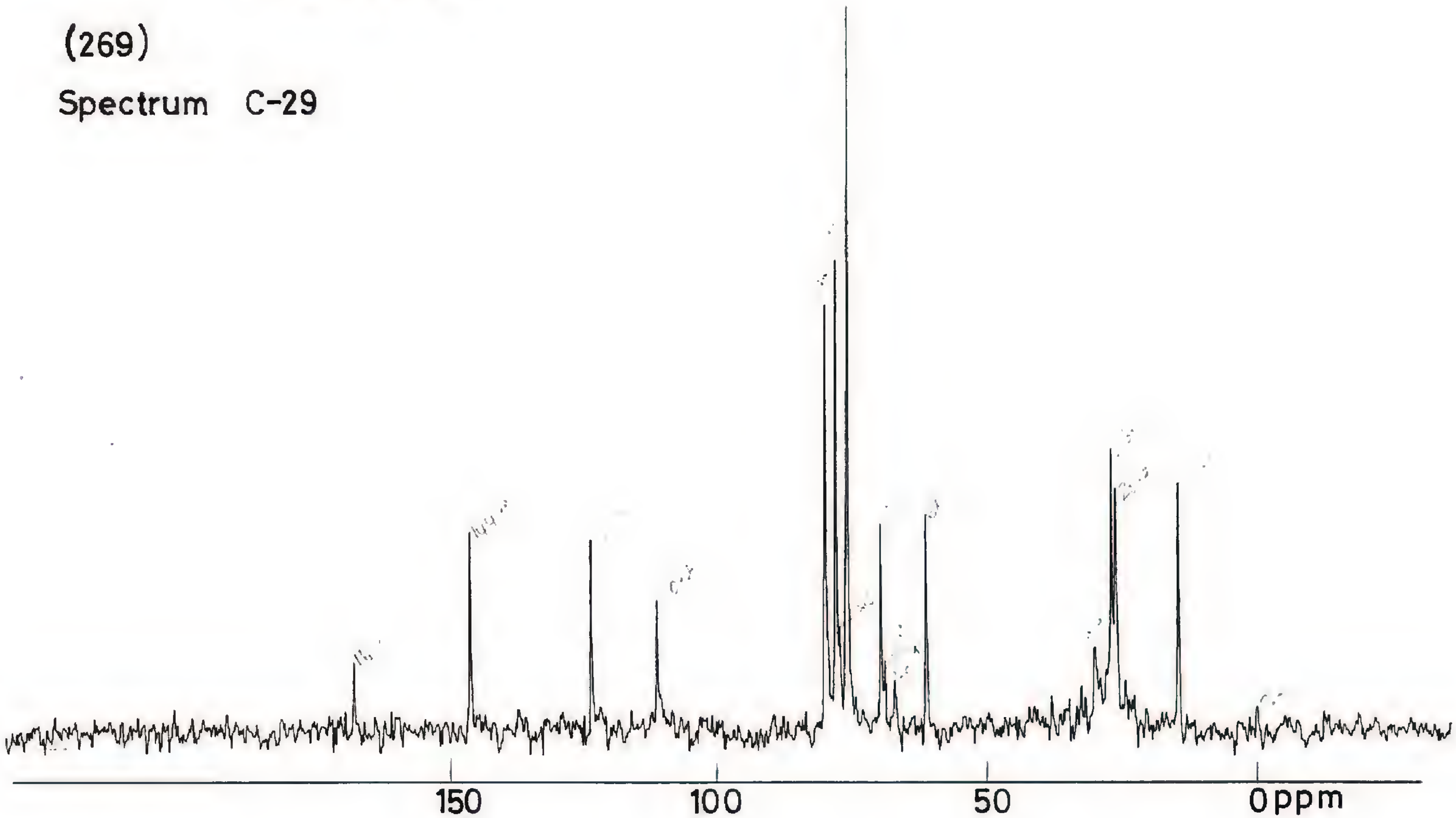
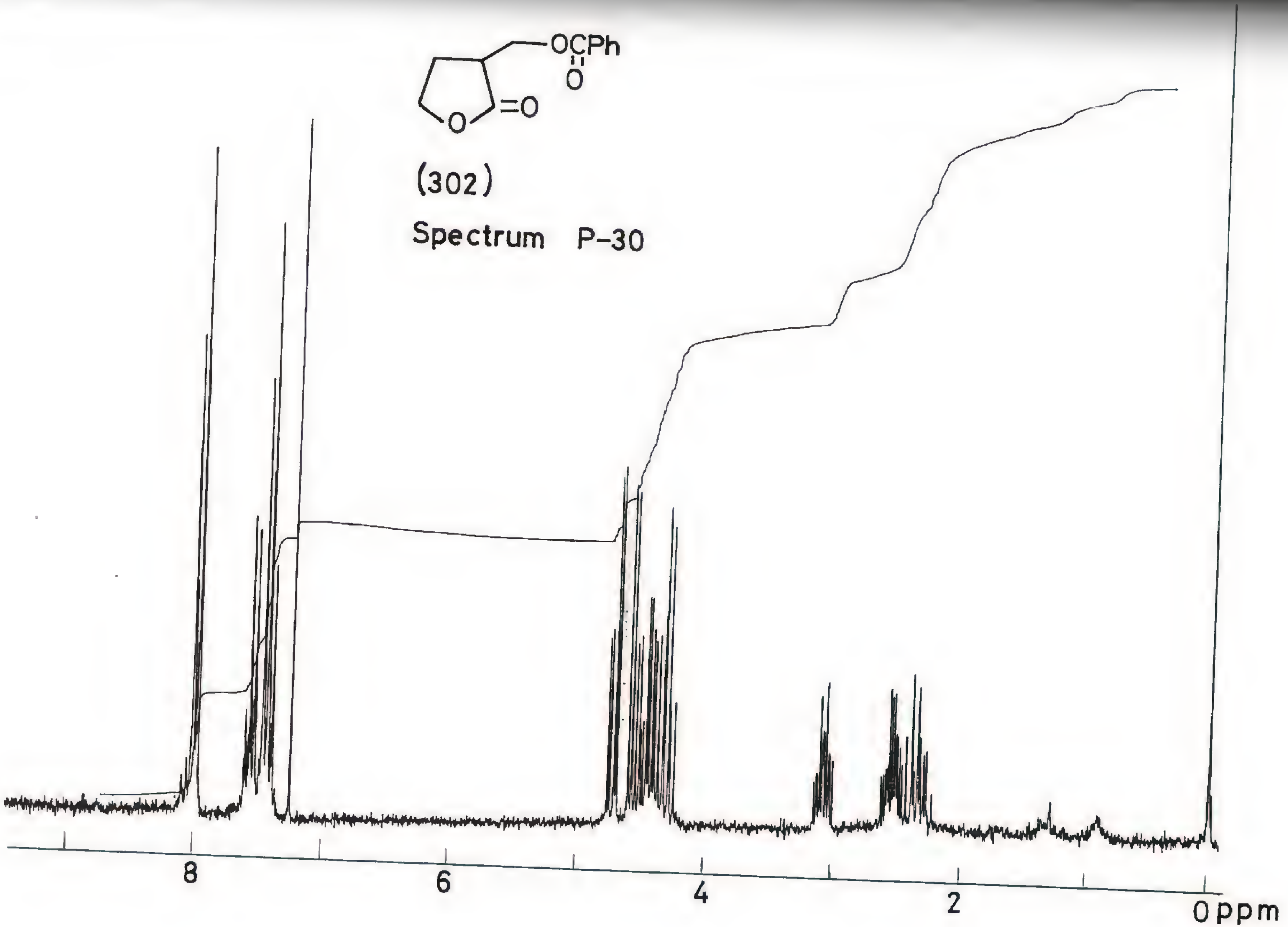
Spectrum C-29





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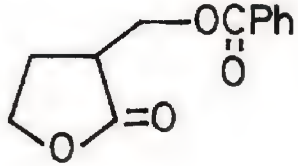
Spectrum P-30



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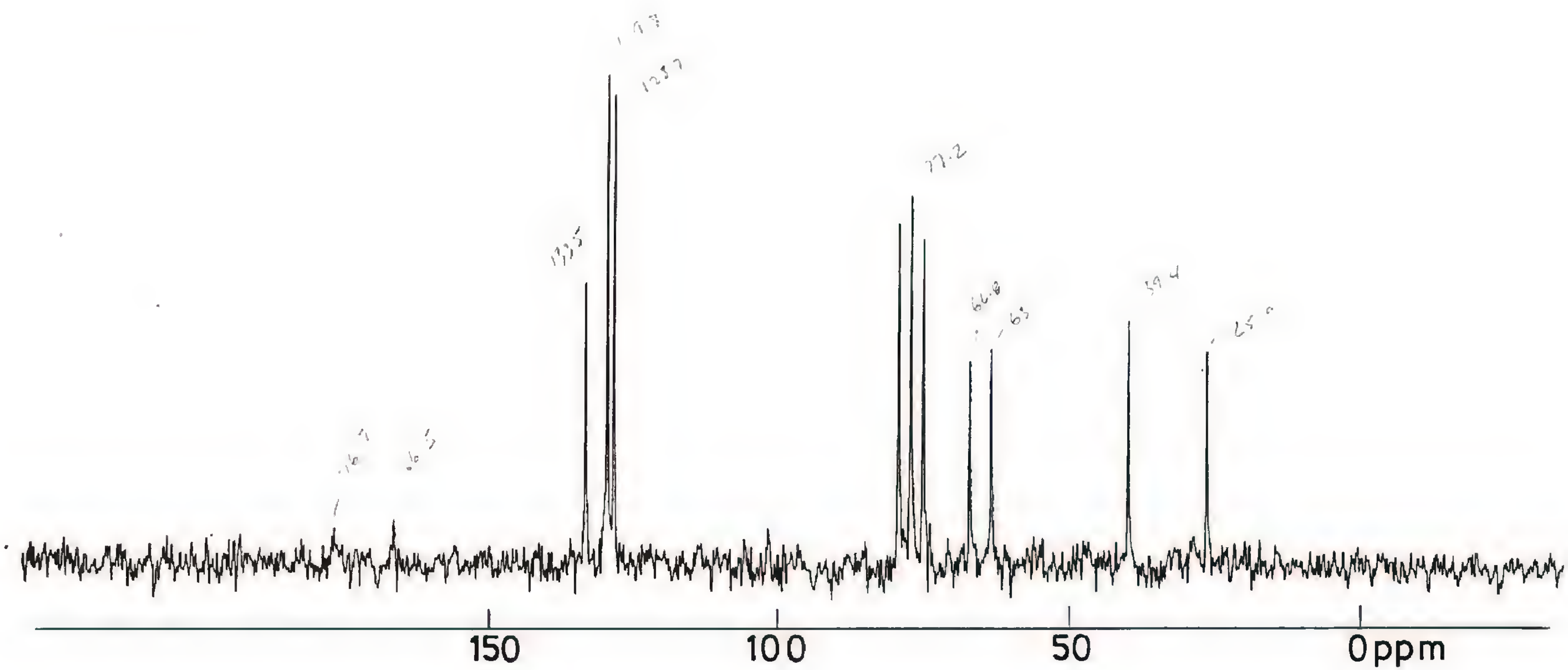
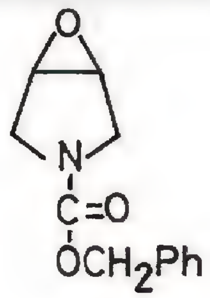
Spectrum C-30





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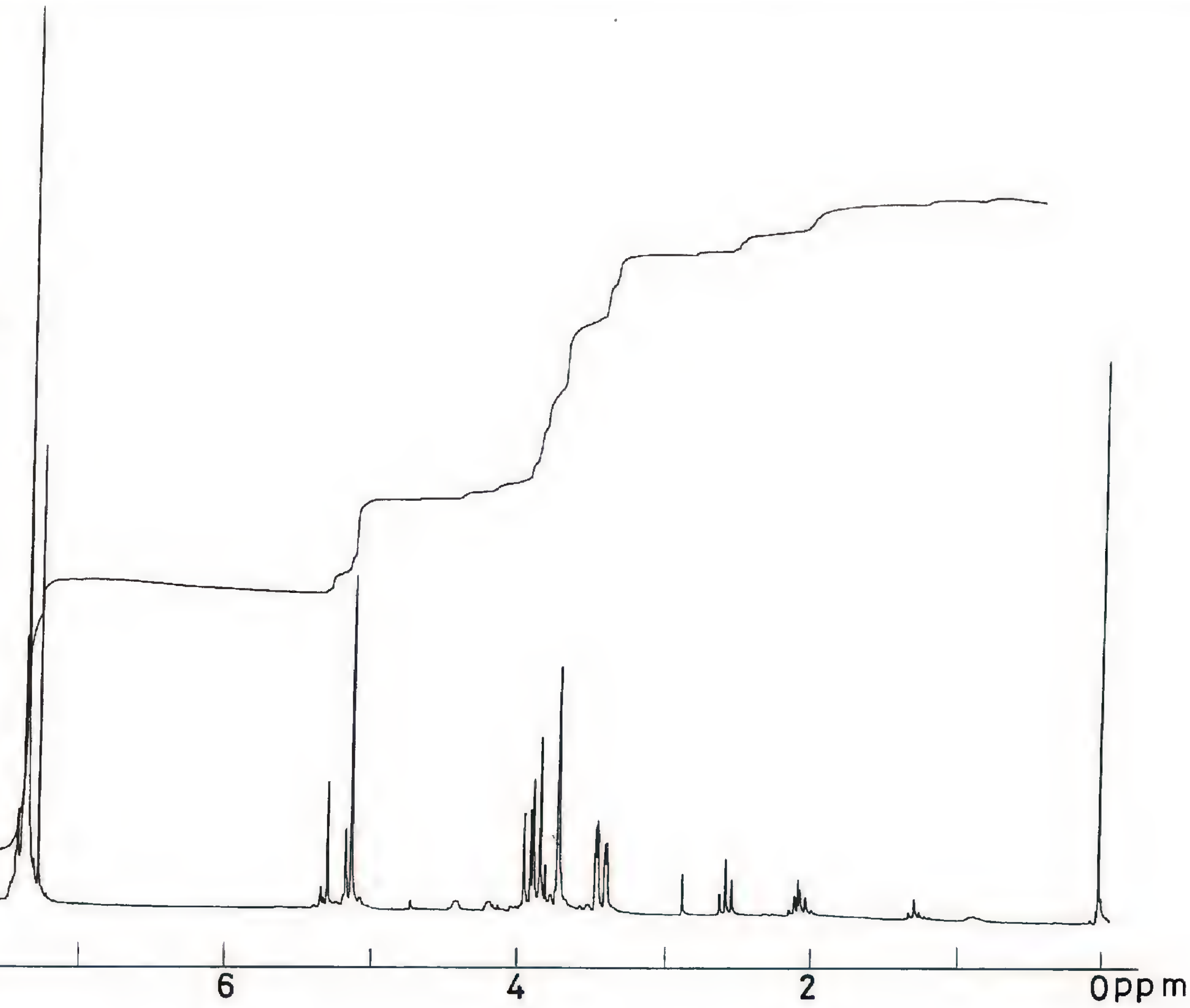
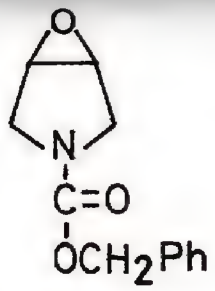
Spectrum P–31





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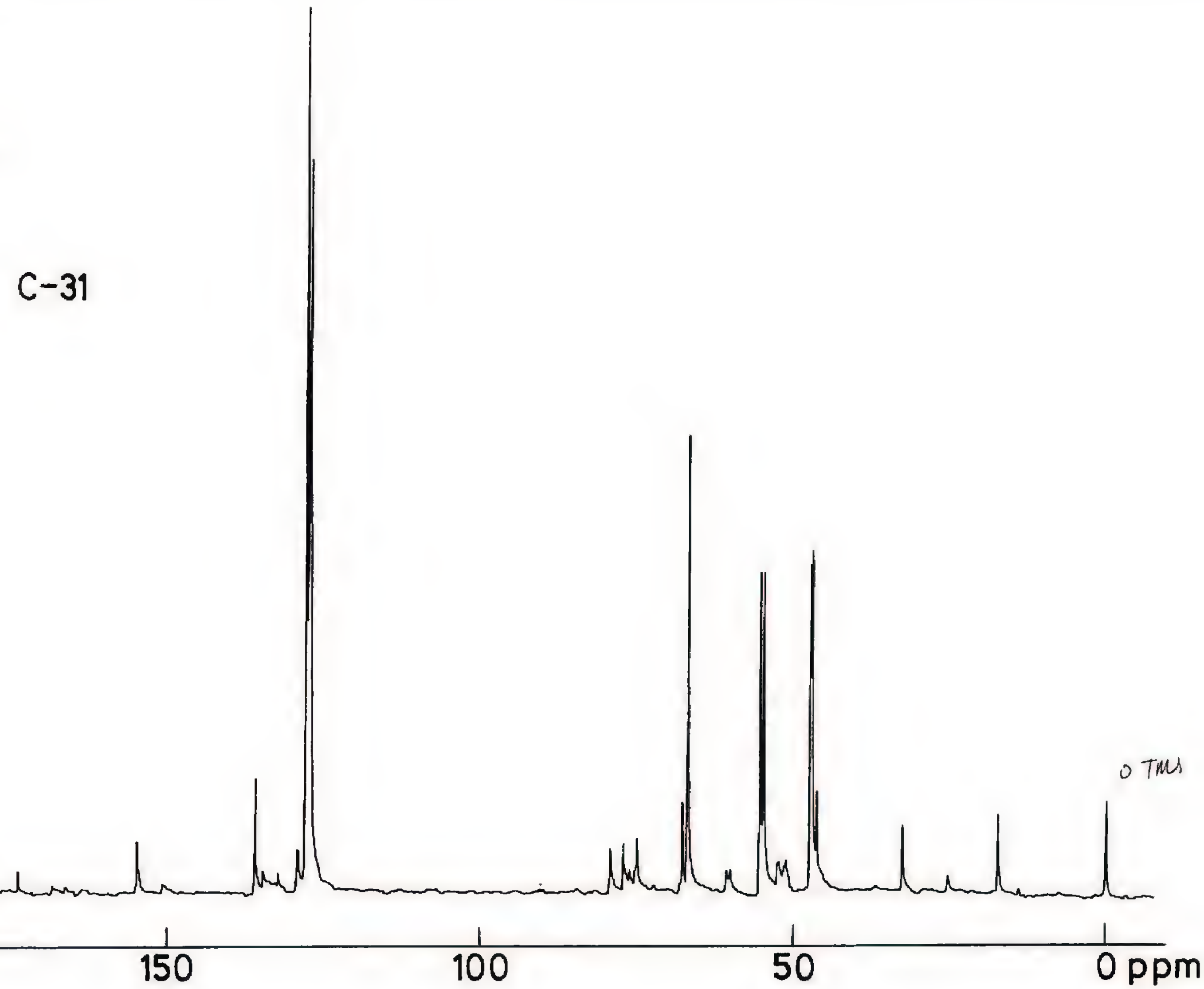
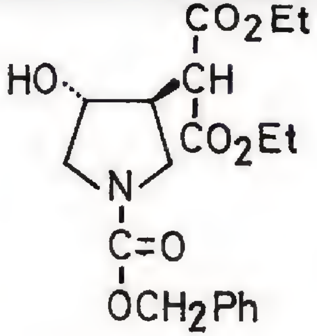
Spectrum C-31





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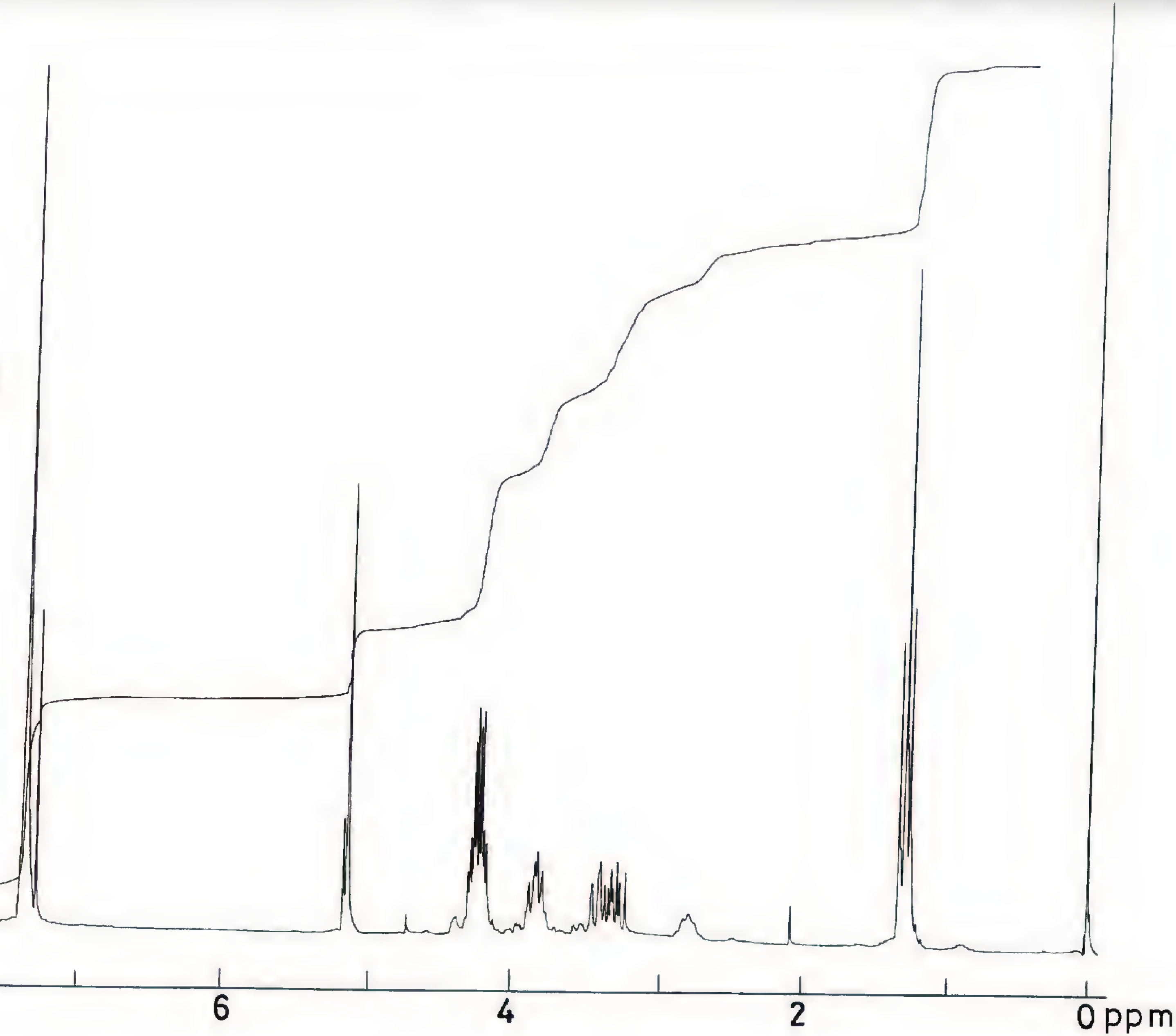
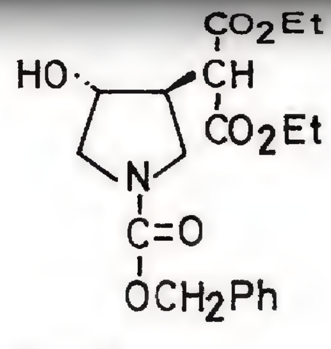
Spectrum P-32





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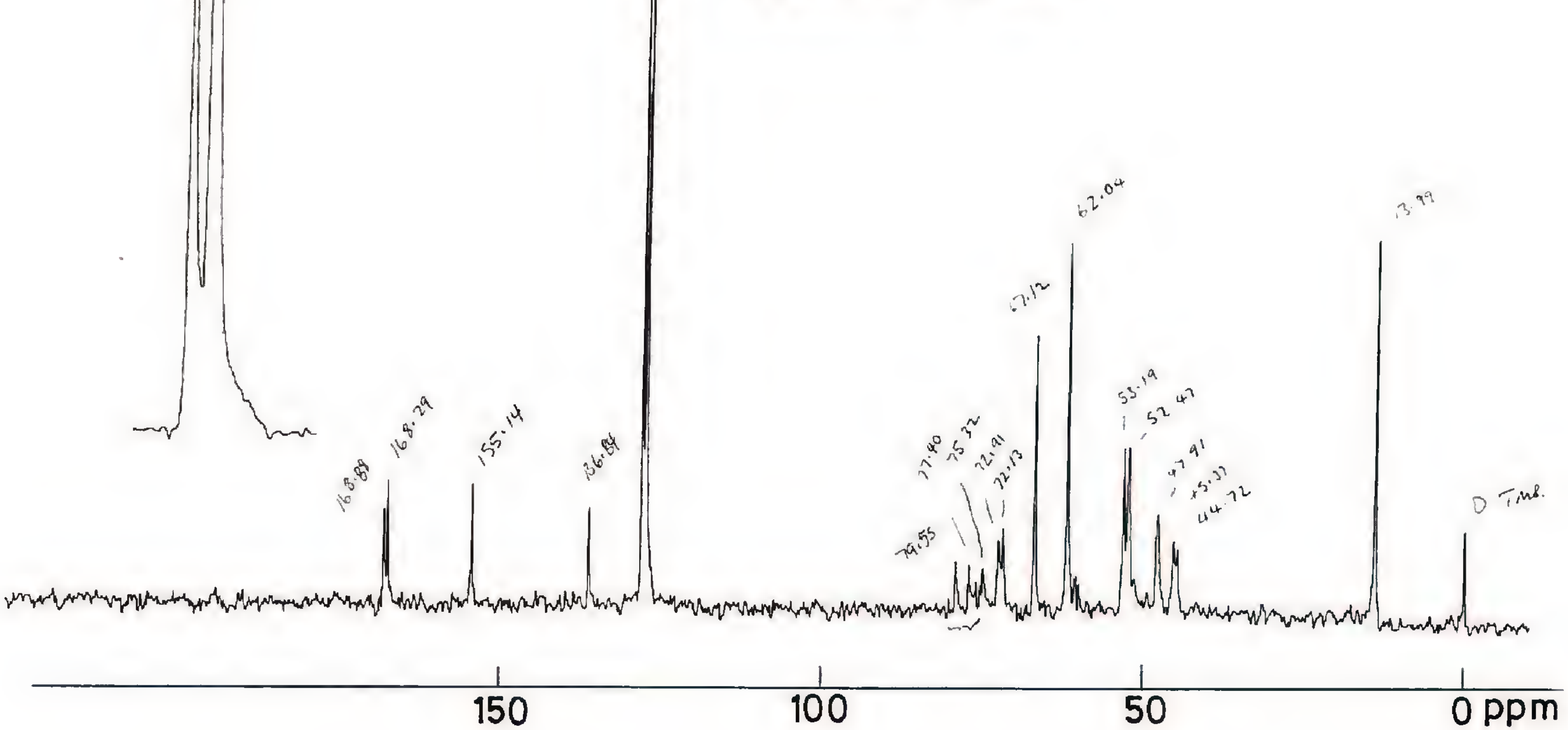
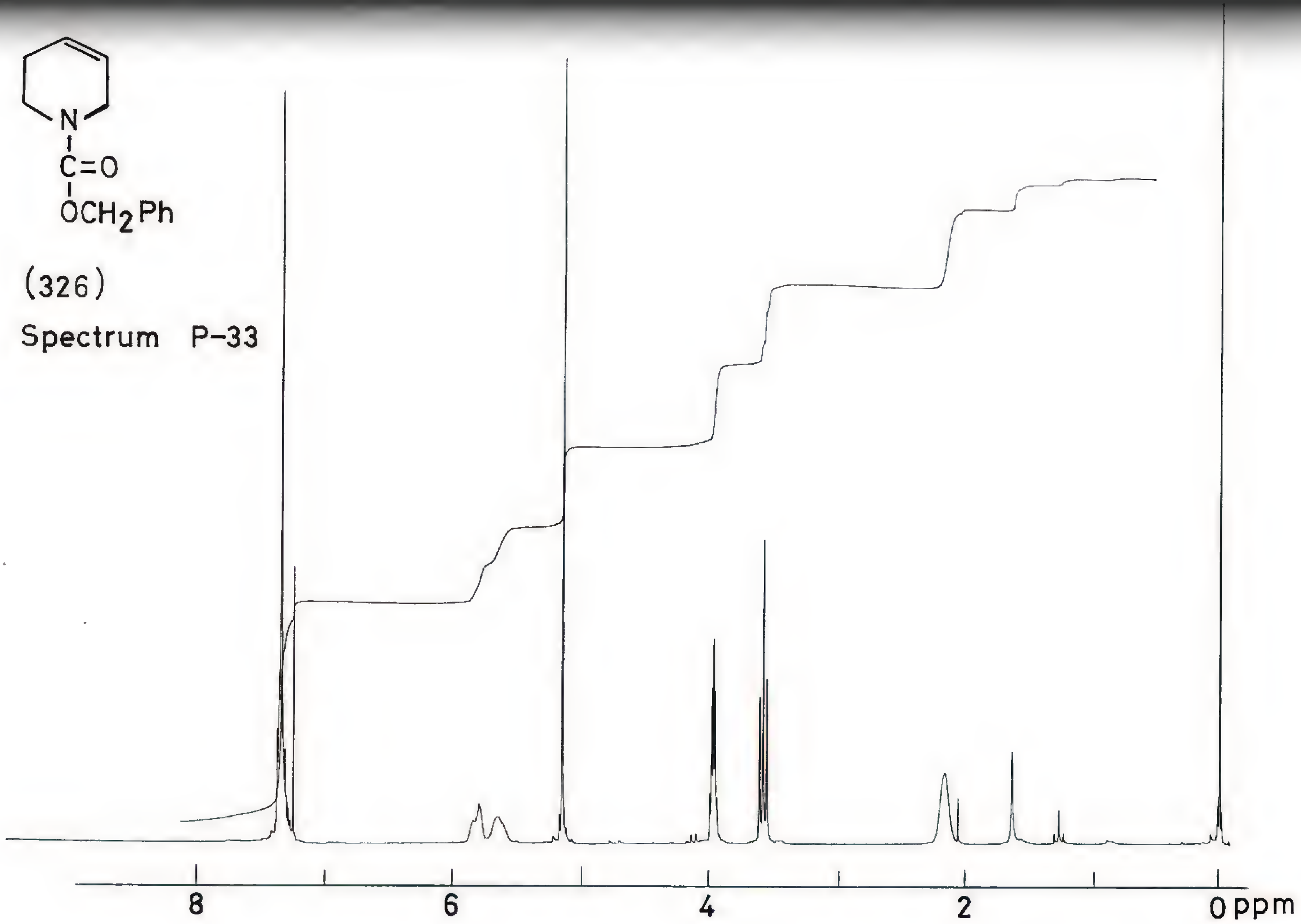
Spectrum C-32





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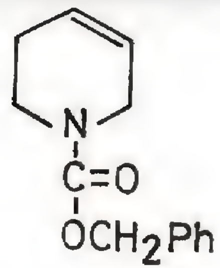
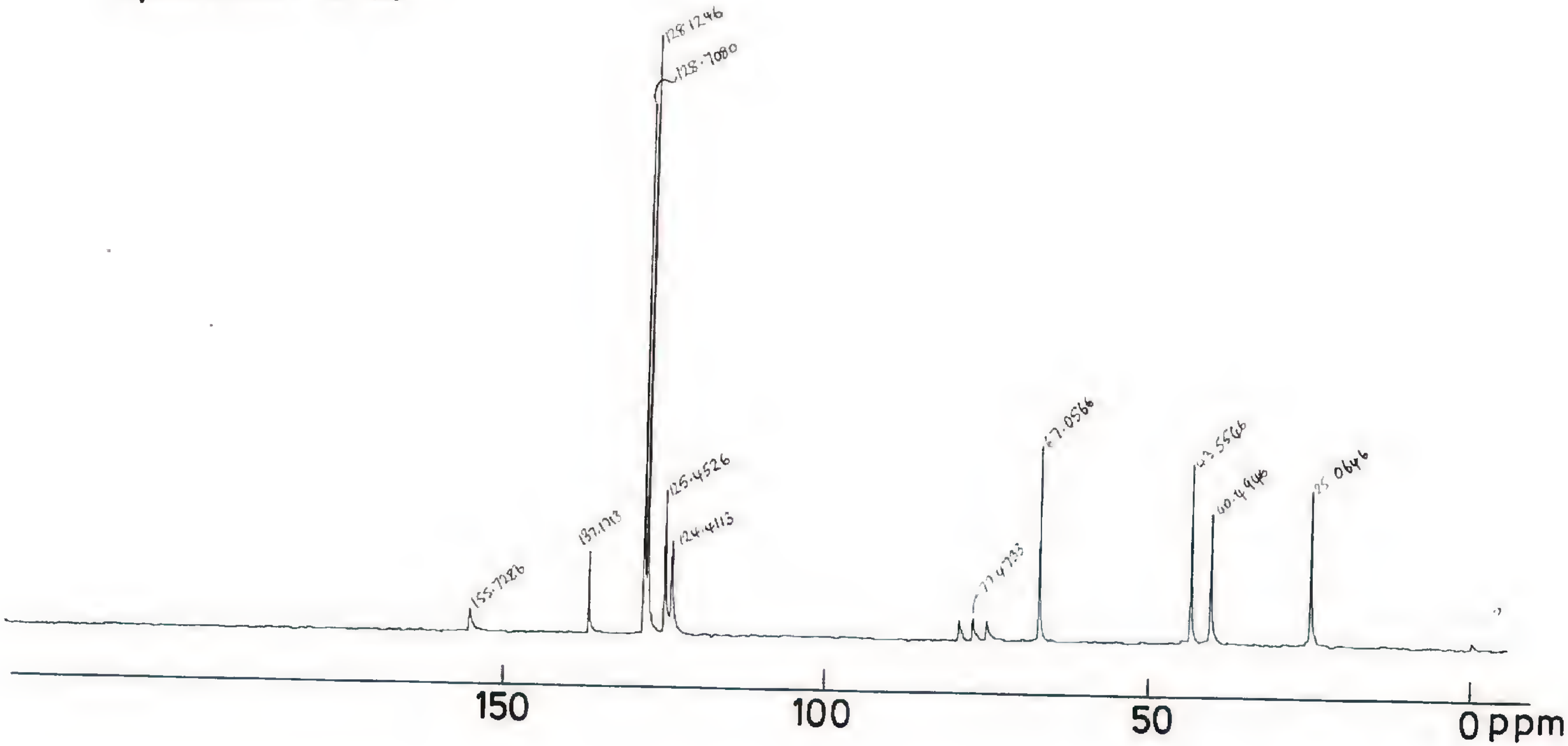
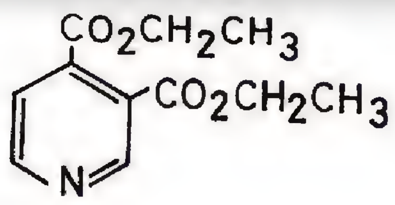
Spectrum P-33



(326)

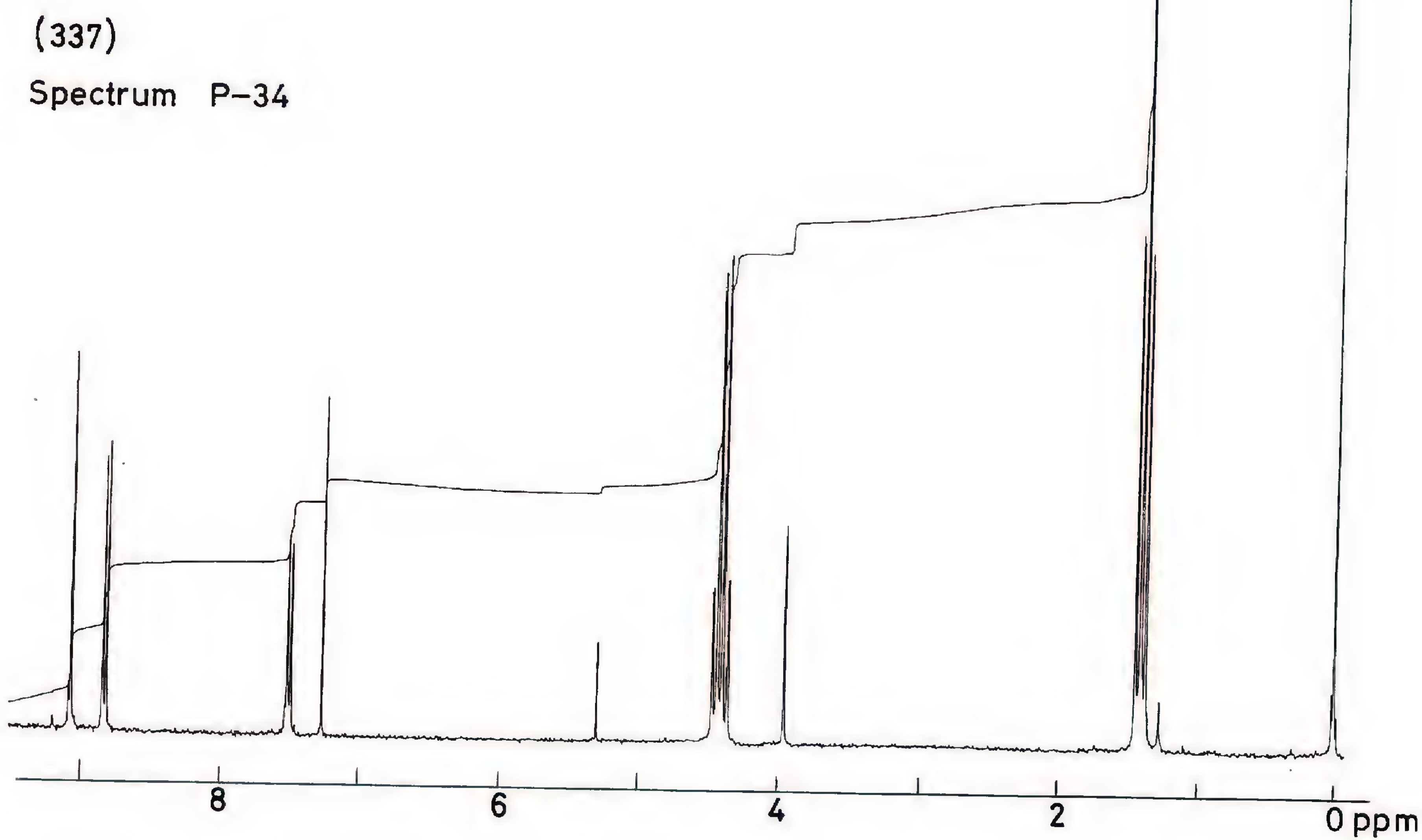
Spectrum C–33

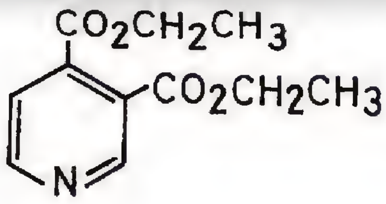




(337)

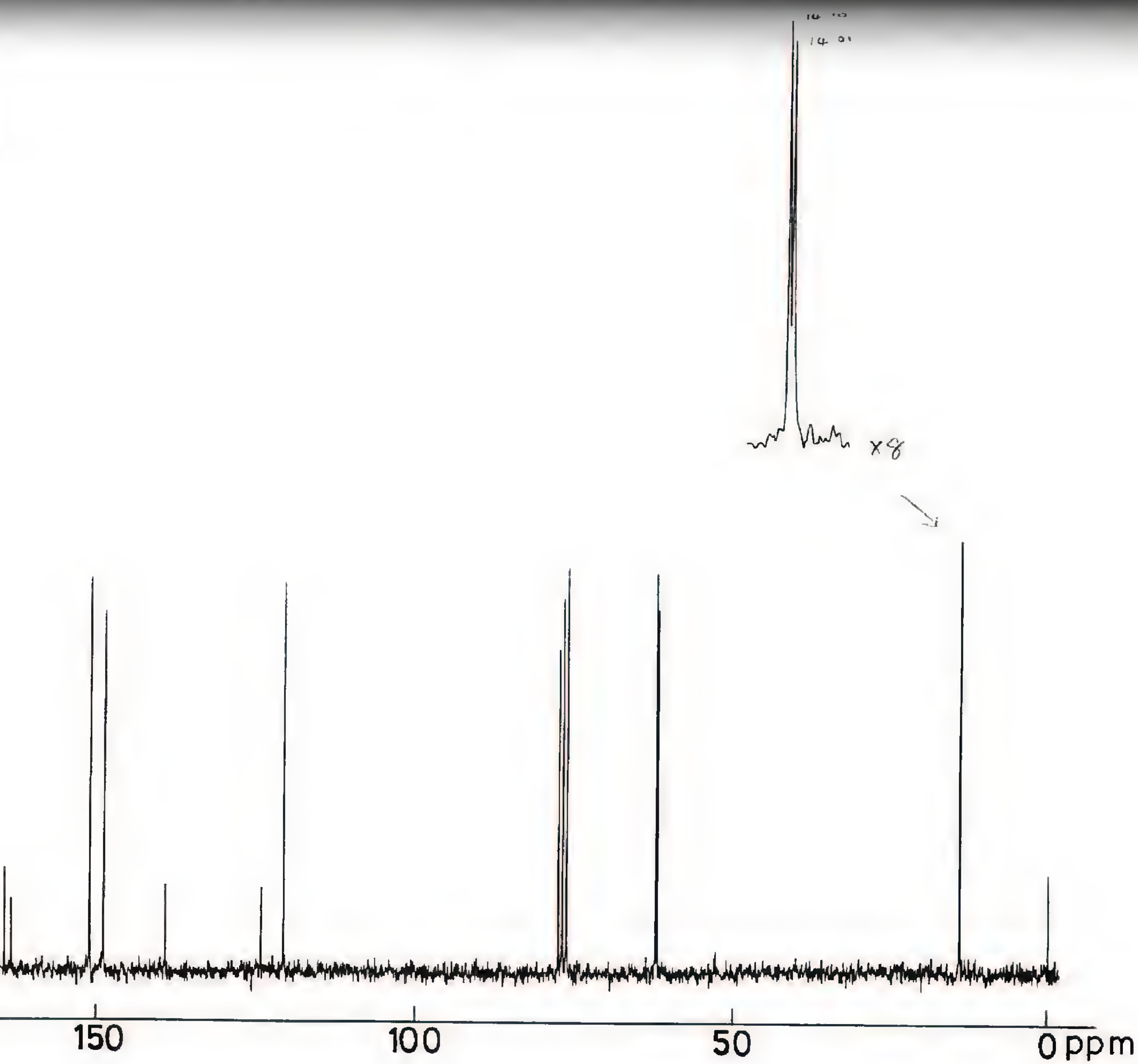
Spectrum P–34

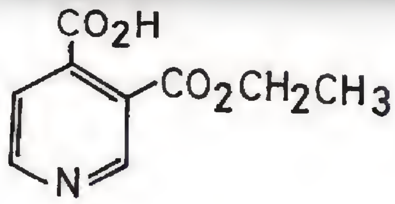




(337)

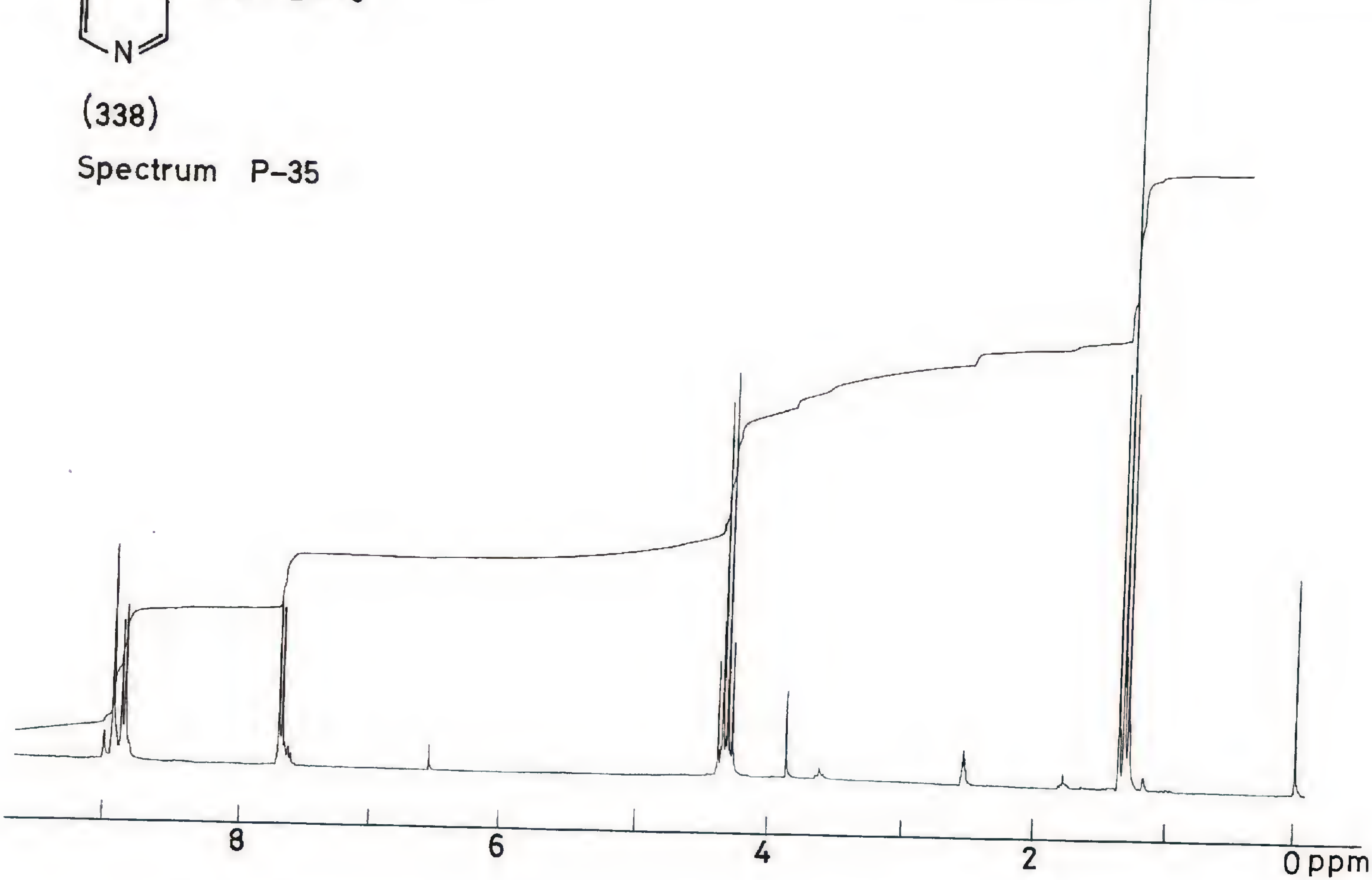
Spectrum C–34

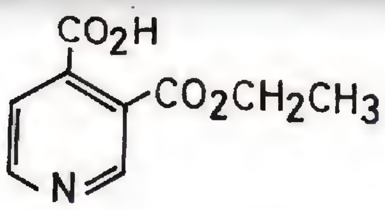




(338)

Spectrum P–35





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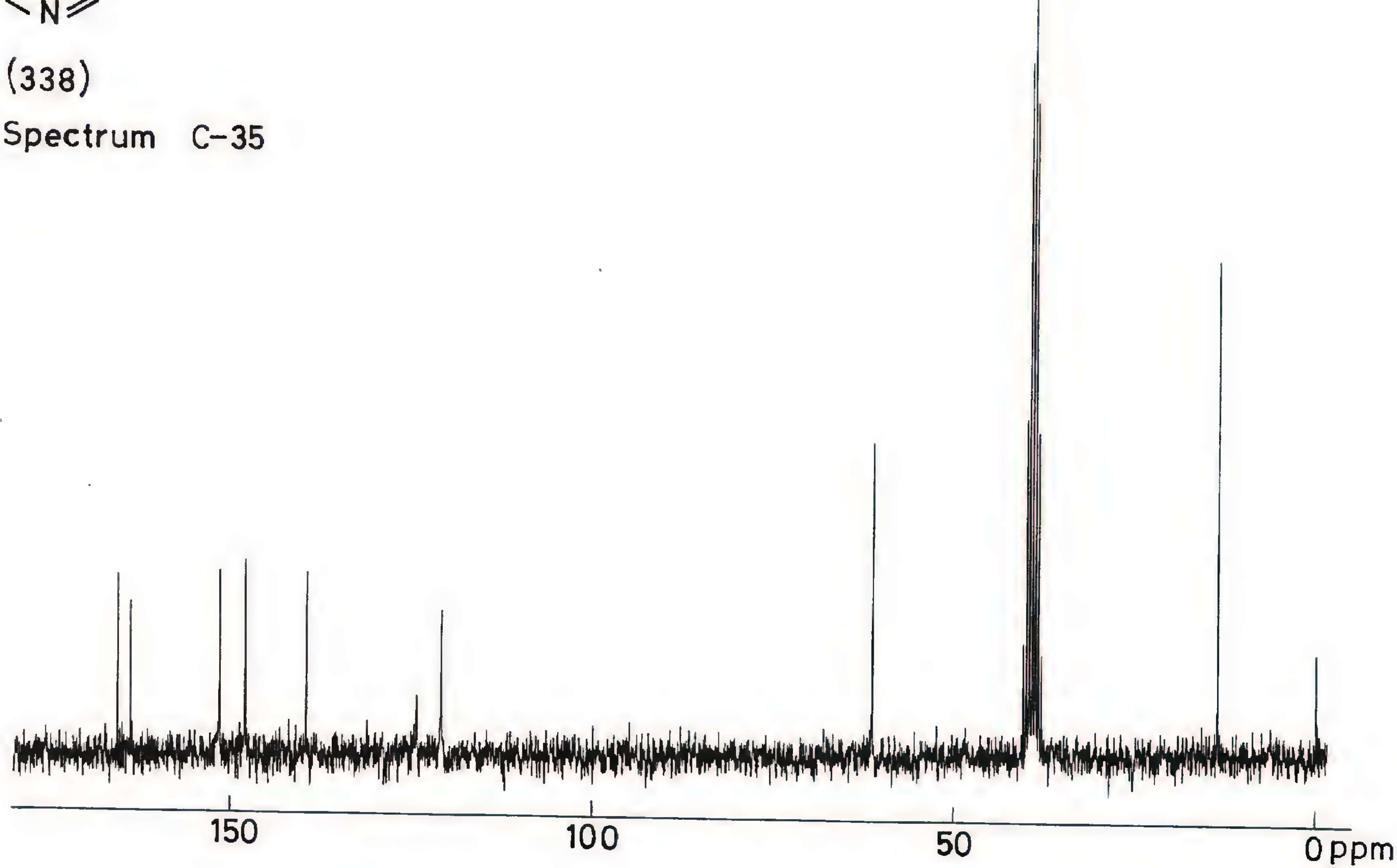
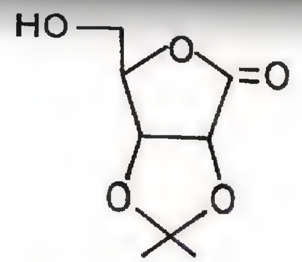
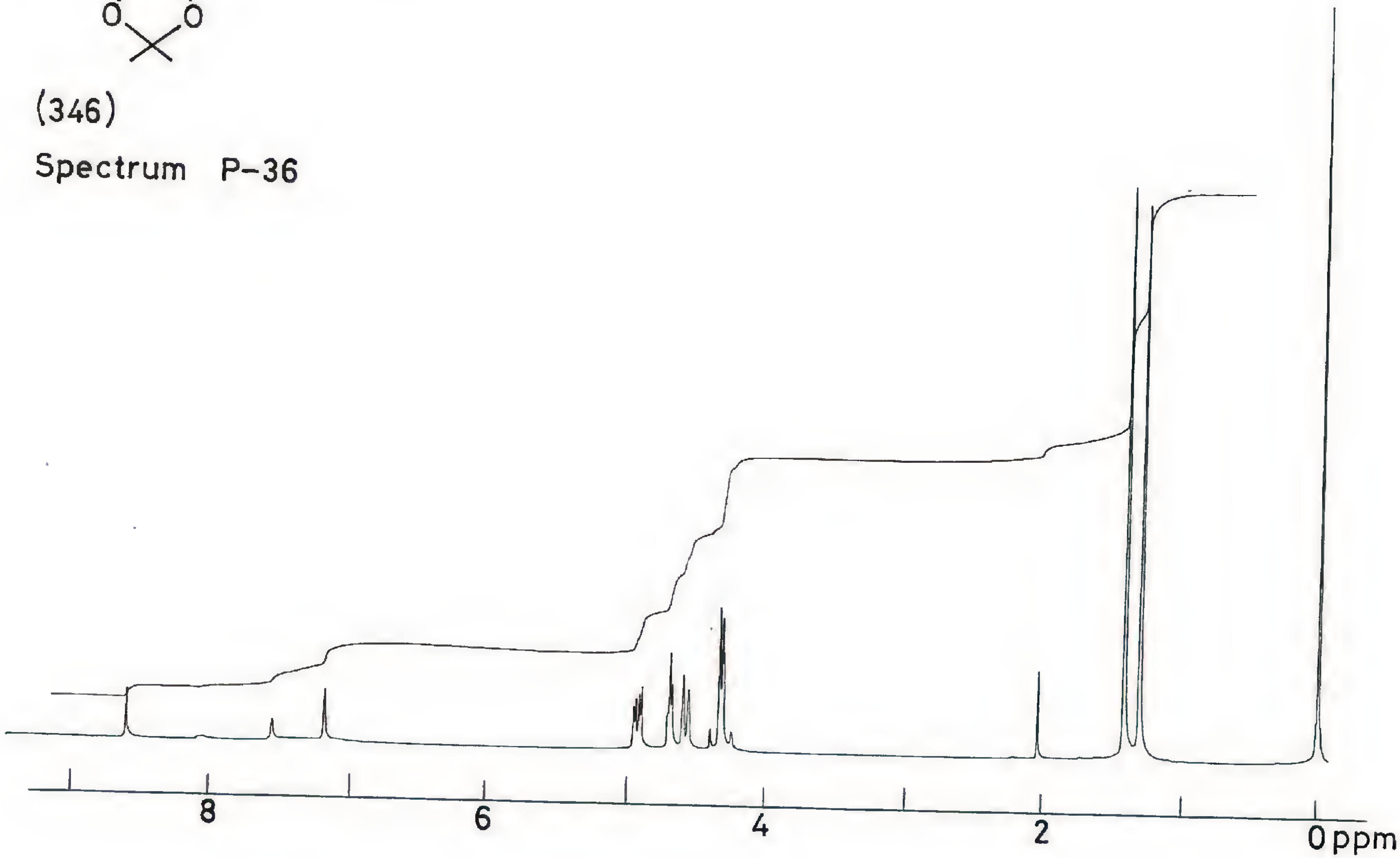
Spectrum C-35

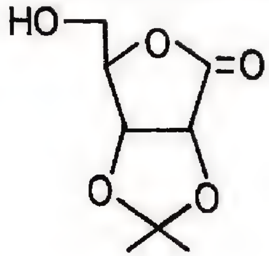




(346)

Spectrum P-36





(346)

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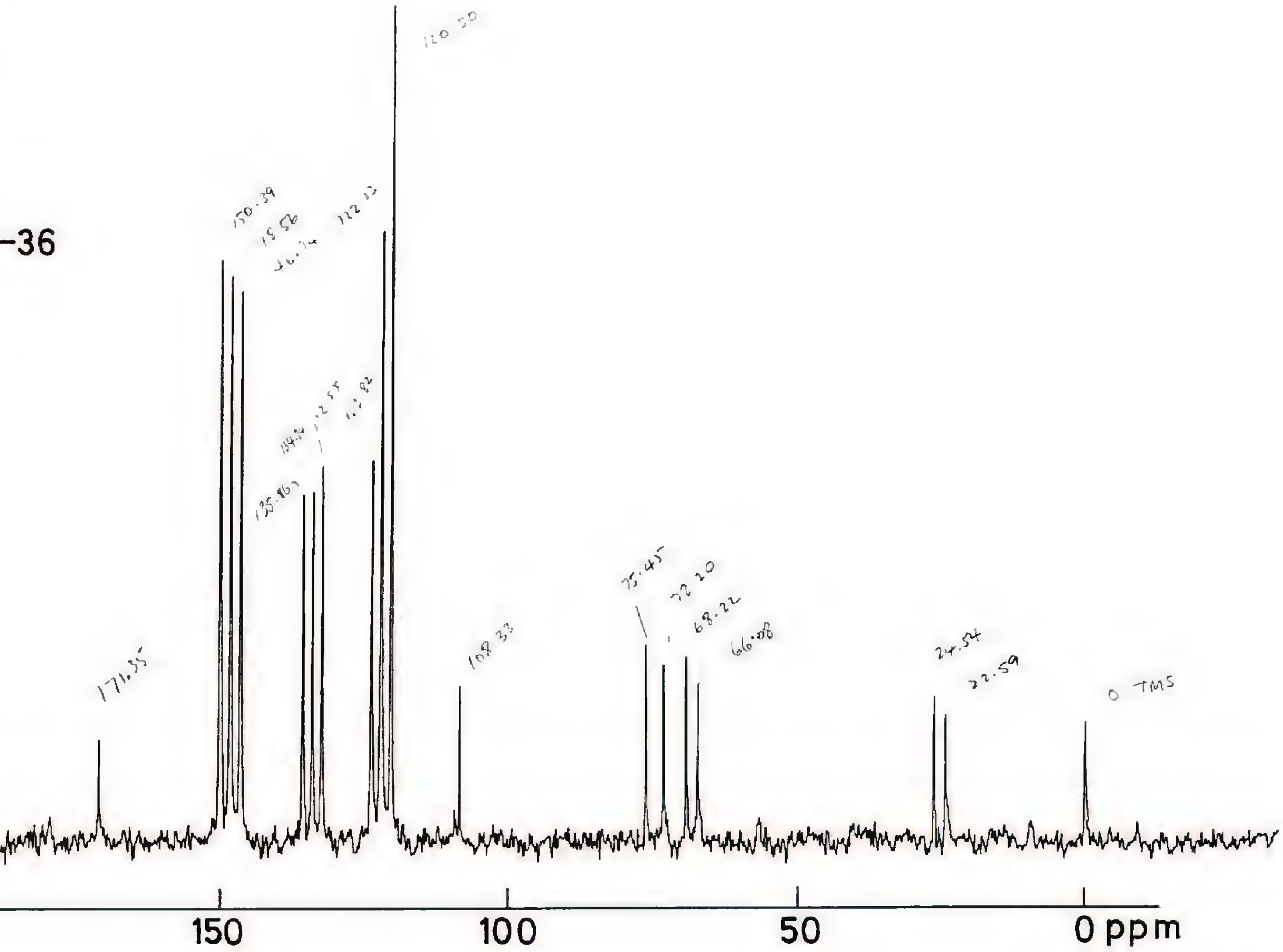

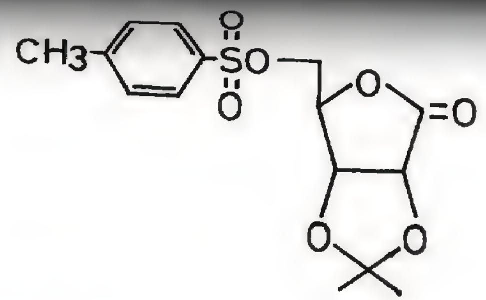

(347)

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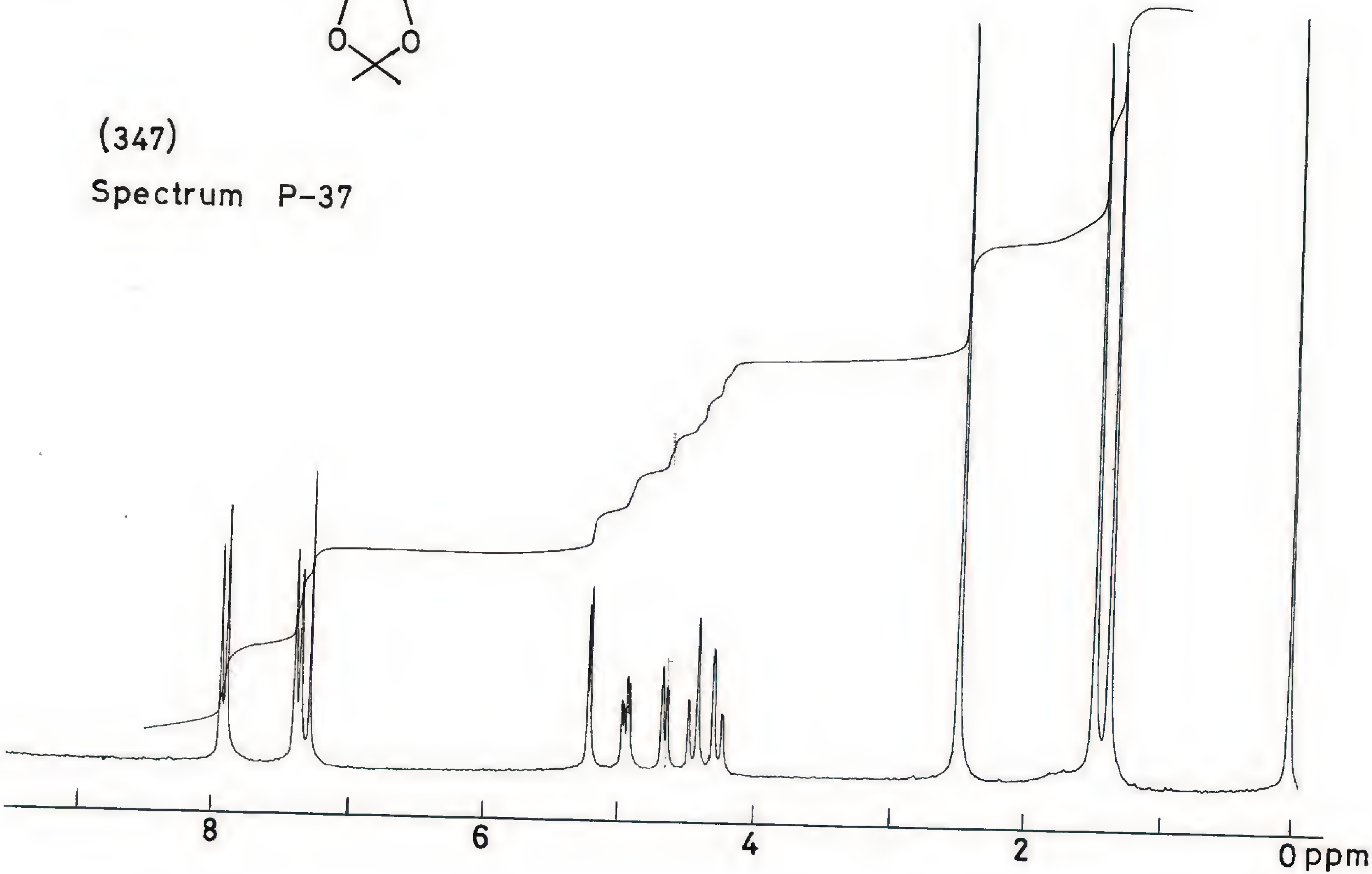

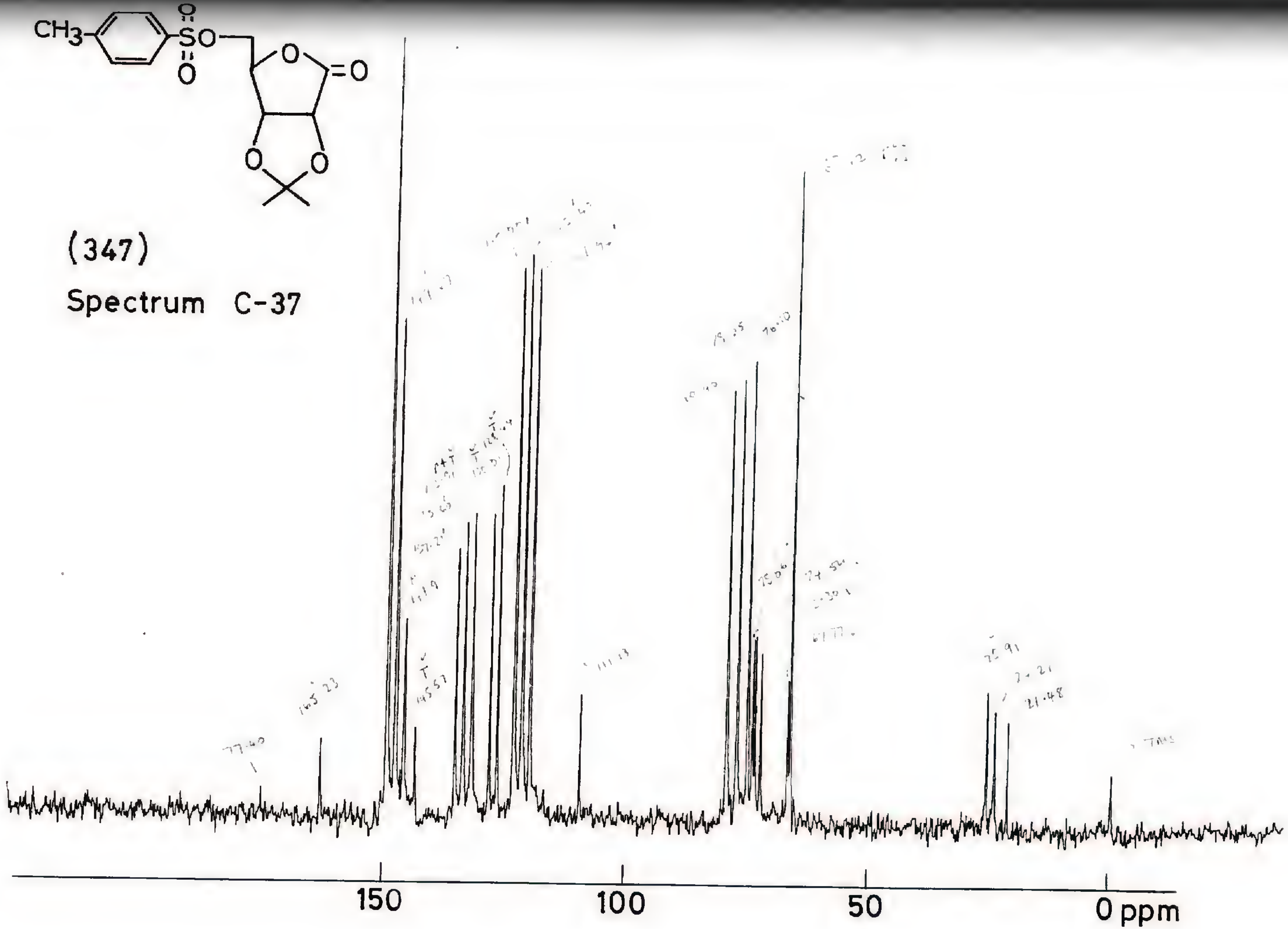

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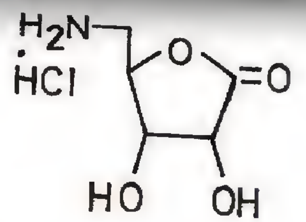
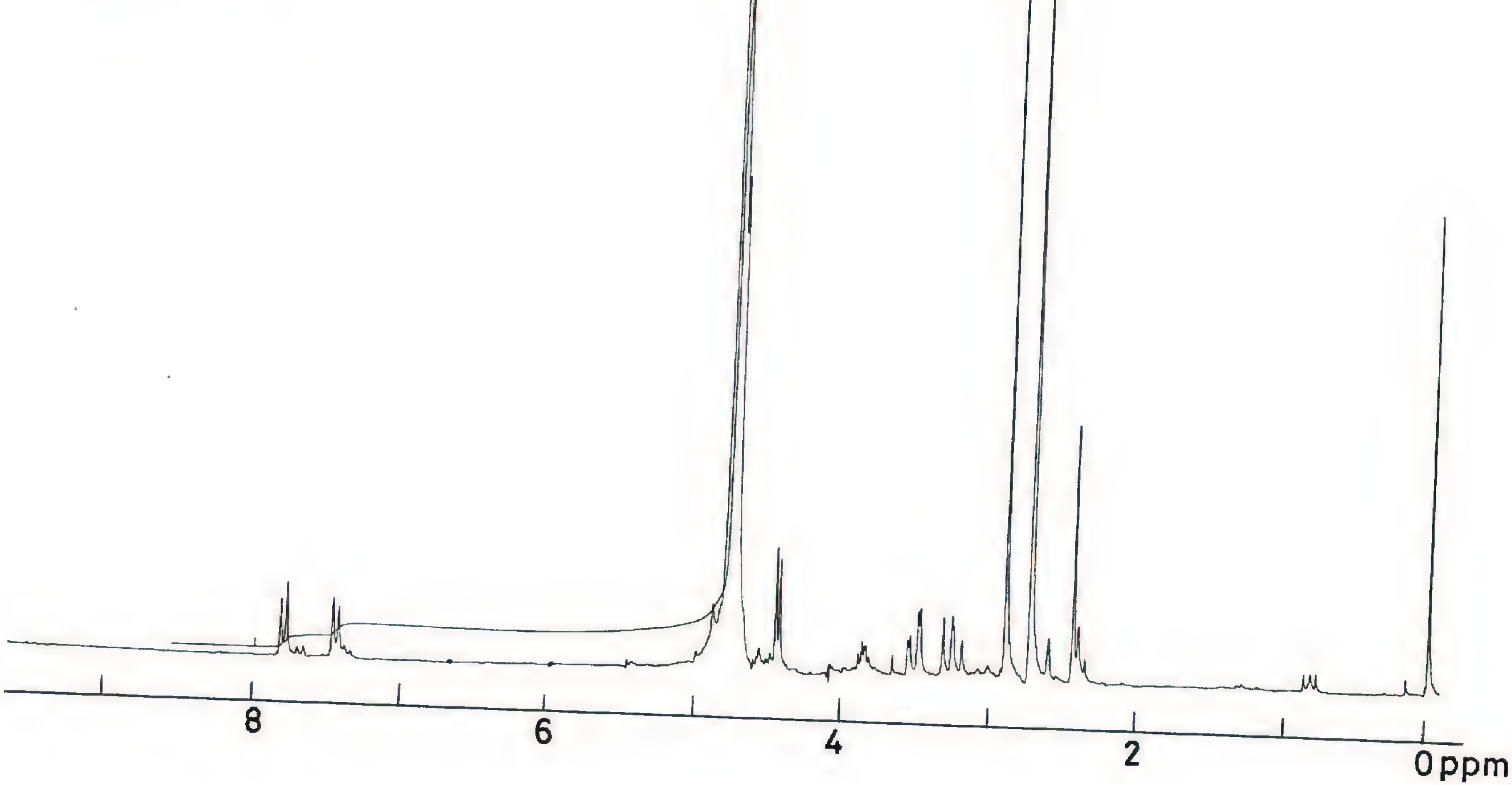
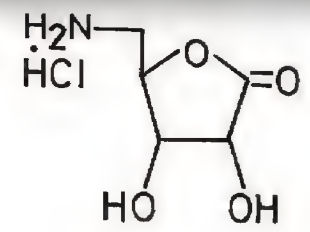


(349)

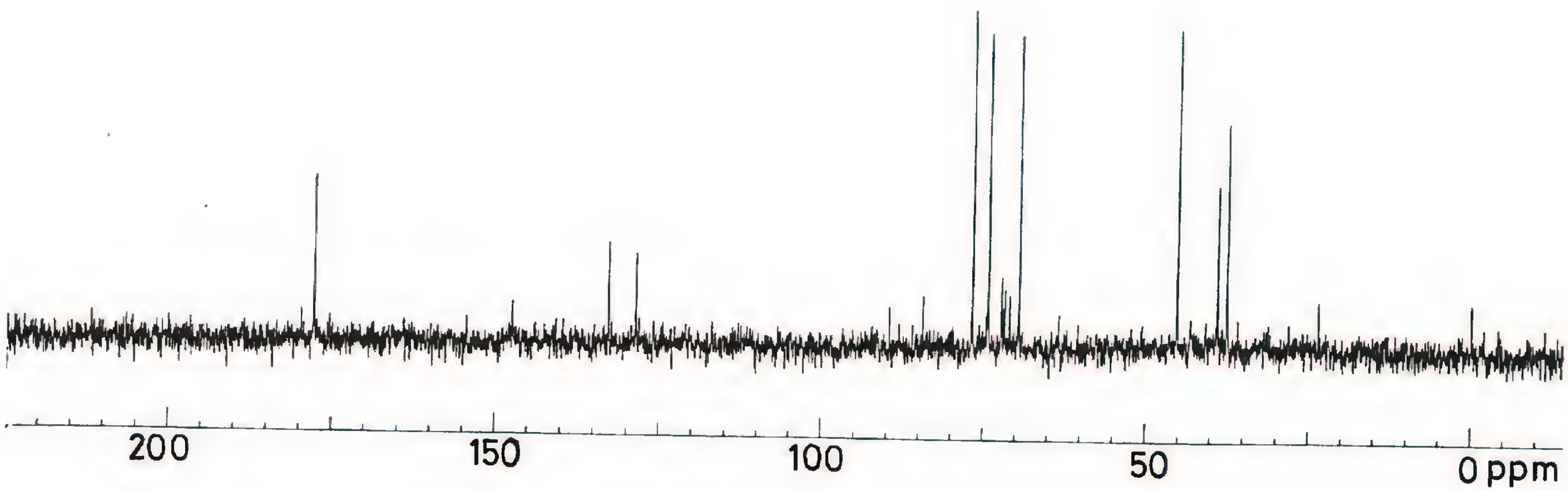
Spectrum P–38

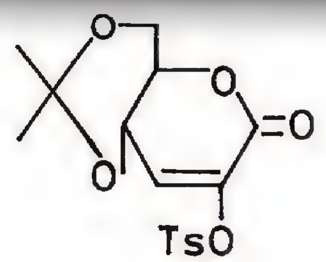




(349)

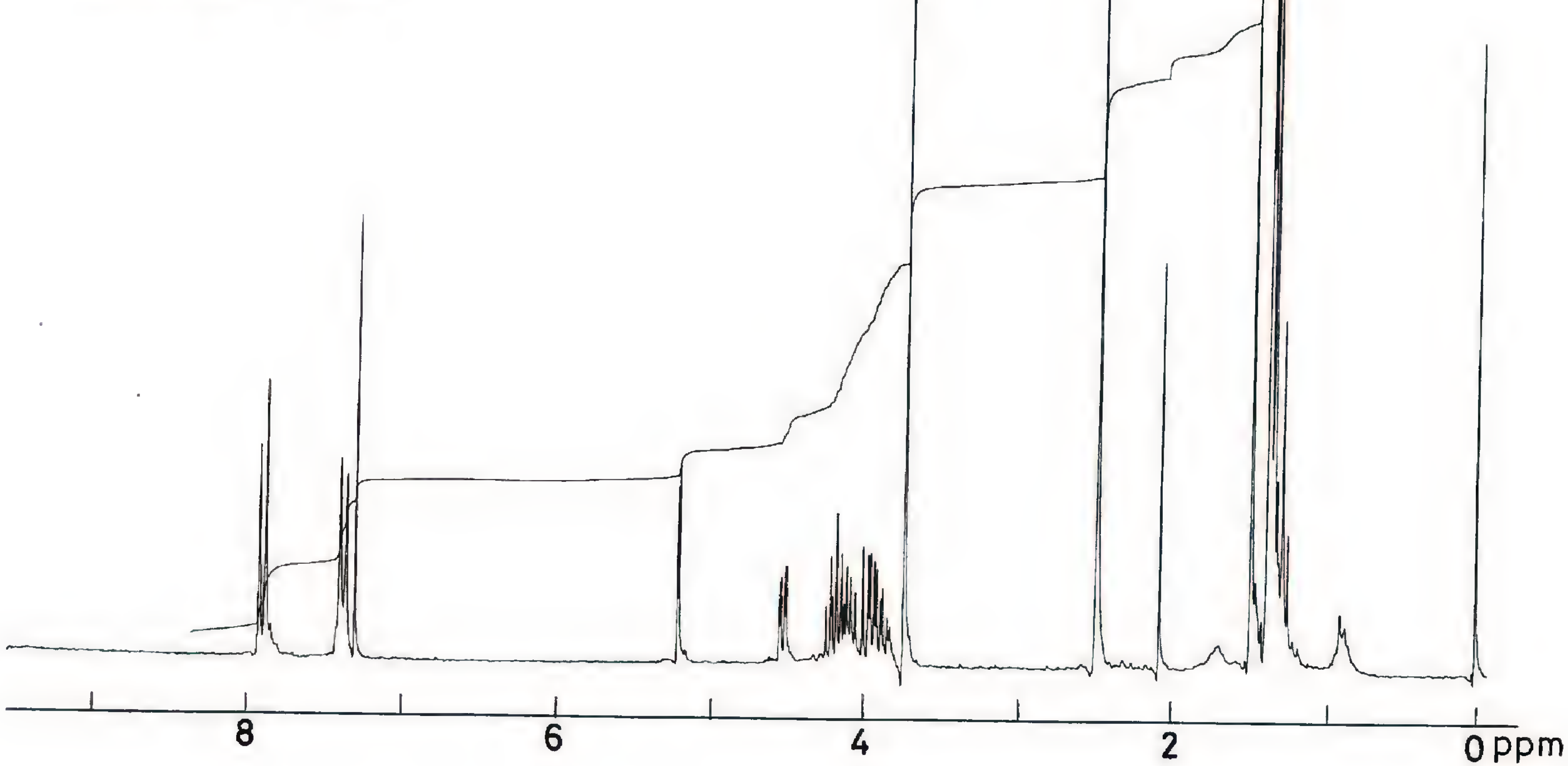
Spectrum C-38

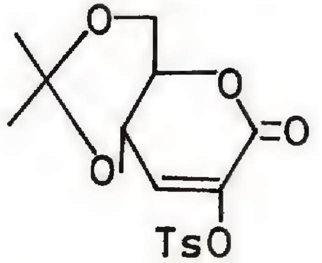




(358)

Spectrum P-39





(358)

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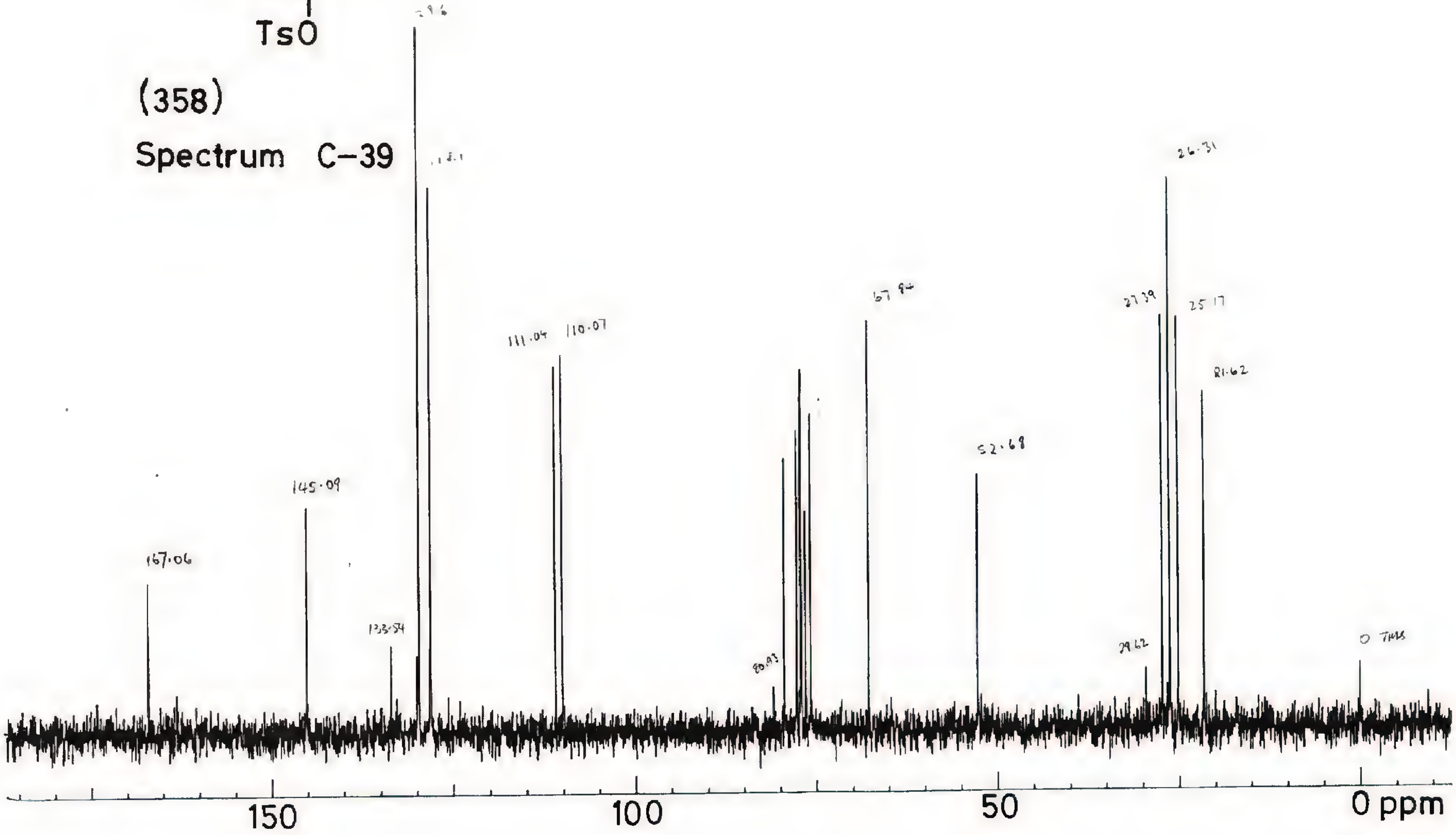

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